A.M.A. Archives OF INTERNAL MEDICINE

FEBRUARY 1956
VOLUME 97 NUMBER 2

Aldosterone in Clinical Medicine—Past, Present, and Future
Jerome W. Conn, Ann Arbor, Mich.

Venous Thrombosis and Obscure Visceral Carcinoma
Samuel Perlow and Jordan L. Daniels, Chicago

Acute Pancreatitis Complicating Diabetes Mellitus
Elaine T. Bossak, New York, and Robert H. Joelson, Paterson, N. J.

On Myelofibrosis
Donald R. Korst, Dallas V. Clatanoff, and Robert F. Schilling, Madison, Wis.

The Treatment of Leprosy
R. G. Cochrane, London

A Comparative Study of the Treatment of Essential Hypertension
Sydney Stonehill, Rochester, N. Y.

Suppression of Gastric Hydrochloric Acid Secretion by Enzyme Inhibitors
Franklin Hollander and Henry D. Janowitz, New York

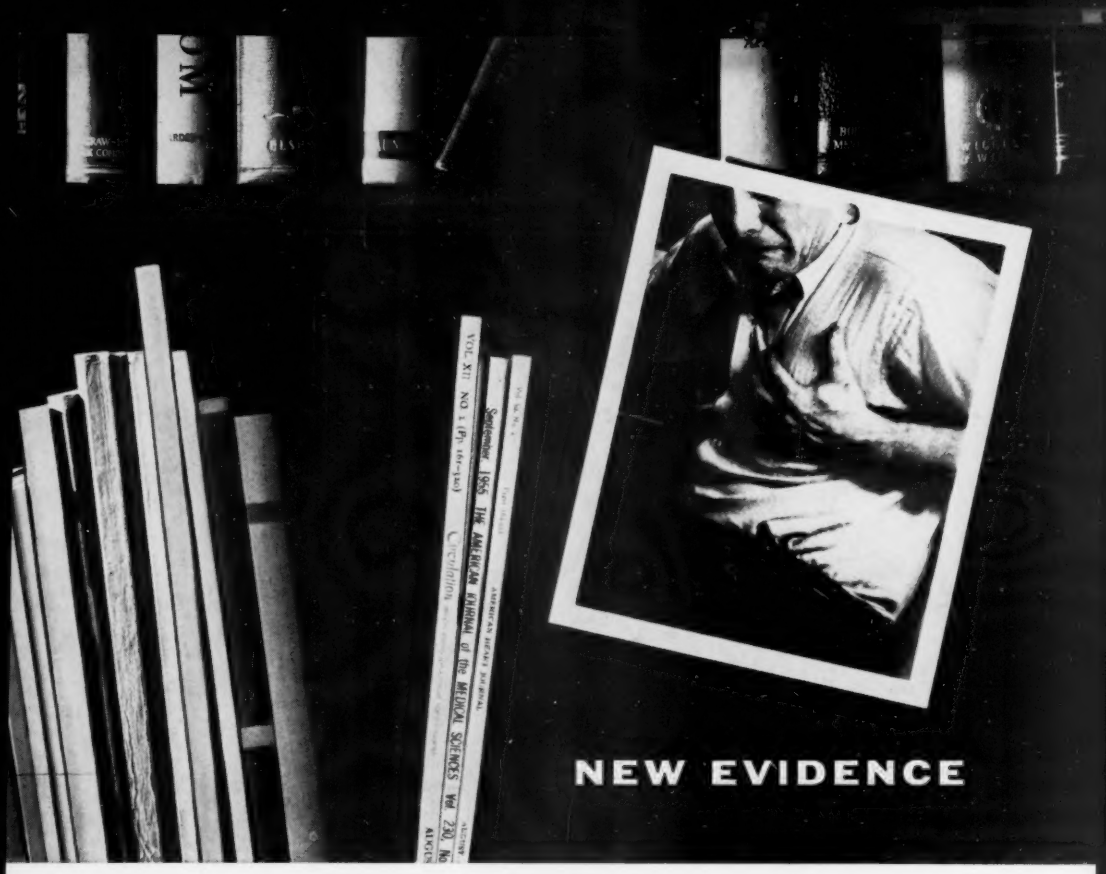
Studies on the Destruction of Red Blood Cells
John W. Harris, Henry H. Brewster, Thomas Hale Ham, and William B. Castle, Boston

Syphilis
Herman Beerman, Ira L. Schamberg, Leslie Nicholas, and Marvin S. Greenberg, Philadelphia

Complete Contents on First Inside Page

AMERICAN MEDICAL ASSOCIATION Publication

EDITORIAL BOARD
PAUL S. RHOADS, Chief Editor, Chicago
WILLIAM B. BEAN, Iowa City
ARTHUR BLOOMFIELD, San Francisco
GEORGE E. BURCH, New Orleans
HUGH R. BUTT, Rochester, Minn.
CHARLES S. DAVIDSON, Boston
LOUIS LEITER, New York
BRUCE K. WISEMAN, Columbus, Ohio



How you can prevent attacks of angina pectoris

Three new studies have recently been added to the extensive investigation of Peritrate's effectiveness in preventing attacks of angina pectoris:

For some patients, state Rosenberg and Michelson, Peritrate "may mean the difference between complete, or almost complete, absence of symptoms, or a prolonged illness with much suffering." *Am. J. M. Sc.* 230:*254 (Sept.) 1955.*

"Impressive and sustained improvement" was also observed in a small number of patients treated by Kory *et al., Am. Heart J.* 50:*308 (Aug.) 1955.*

Peritrate, as evaluated by Russek's group, "was found to exert a marked modifying influence . . ." on EKGs and ". . . exhibited its action up to five hours or more following administration. . . ." *Circulation* 12:*169 (Aug.) 1955.*

By prescribing Peritrate on a continuous daily dosage schedule (10 or 20 mg. 4 times a day) you can diminish the number and severity of attacks . . . reduce nitroglycerin dependence . . . increase exercise tolerance . . . improve abnormal EKG findings.

Usual dosage: 10 to 20 mg. *before meals* and at bedtime.

Five convenient dosage forms: *Peritrate* 10 mg. and 20 mg.; *Peritrate Delayed Action* (10 mg.) for extended protection at night; *Peritrate with Phenobarbital* (10 mg. with phenobarbital 15 mg.) where sedation is also required; *Peritrate with Aminophylline* (10 mg. with 100 mg. aminophylline) in cardiac and circulatory inadequacy.

Peritrate®

(BRAND OF PENTAERYTHRITOL TETRANITRATE)

WARNER-CHILCOTT

TABLE OF CONTENTS

VOLUME 97 FEBRUARY 1956 NUMBER 2

ORIGINAL ARTICLES

PAGE

Aldosterone in Clinical Medicine—Past, Present, and Future
Jerome W. Conn, M.D., Ann Arbor, Mich. ... 135

Studies on the Destruction of Red Blood Cells
John W. Harris, M.D.; Henry H. Brewster, M.D.; Thomas Hale Ham, M.D., Cleveland, and William B. Castle, M.D., Boston ... 145

On Myelofibrosis
Donald R. Korst, M.D.; Dallas V. Clatanoff, M.D., and Robert F. Schilling, M.D., Madison, Wis. ... 169

Venous Thrombosis and Obscure Visceral Carcinoma
Samuel Perlow, M.D., and Jordan L. Daniels, M.D., Chicago ... 184

A Comparative Study of the Treatment of Essential Hypertension
Sydney Stonehill, M.D., Rochester, N. Y. ... 189

Suppression of Gastric Hydrochloric Acid Secretion by Enzyme Inhibitors
Franklin Hollander, Ph.D., and Henry D. Janowitz, M.D., New York ... 194

Acute Pancreatitis Complicating Diabetes Mellitus
Elaine T. Bossak, M.D., New York, and Robert H. Joelson, M.D., Paterson, N. J. ... 201

TREATMENT IN INTERNAL MEDICINE

The Treatment of Leprosy
R. G. Cochrane, M.D., F.R.C.P., D.T.M. & M., London ... 208

PROGRESS IN INTERNAL MEDICINE

Syphilis
Herman Beerman, M.D.; Ira L. Schamberg, M.D.; Leslie Nicholas, M.D., and Marvin S. Greenberg, M.D., Philadelphia, with the Collaboration of T. Guthe, M.D., and C. J. Hackett, M.D., Geneva, Switzerland ... 215

CASE REPORTS

Pulmonary Infarction Complicating Mumps
Capt. Leroy J. Young (MC), and Major Ray G. Cowley (MC), U. S. Army ... 249

Disseminated Actinomycosis Treated with Tetracycline
William J. Martin, M.D.; Donald R. Nichols, M.D.; William E. Wellman, M.D., and Lyle A. Weed, M.D., Rochester, Minn. ... 252

REGULAR DEPARTMENTS

News and Comment ... 259

Books

Books Received ... 261

Book Reviews ... 261

A. M. A.
ARCHIVES OF INTERNAL MEDICINE

VOLUME 97 FEBRUARY 1956 NUMBER 2

COPYRIGHT, 1956, BY THE AMERICAN MEDICAL ASSOCIATION

EDITORIAL BOARD

PAUL S. RHOADS, Chief Editor, Chicago

WILLIAM B. BEAN, Iowa City
HUGH R. BUTT, Rochester, Minn.
ARTHUR BLOOMFIELD, San Francisco
CHARLES S. DAVIDSON, Boston
GEORGE E. BURCH, New Orleans
LOUIS LEITER, New York
BRUCE K. WISEMAN, Columbus, Ohio

AUSTIN SMITH, Editor, A. M. A. Scientific Publications
GILBERT S. COOPER, Managing Editor, Specialty Journals

AMERICAN MEDICAL ASSOCIATION SCIENTIFIC PUBLICATIONS

A. M. A. Specialty Journals

Monthly

A. M. A. Archives of Internal Medicine. Paul S. Rhoads, M.D., Chief Editor, American Medical Association, 535 N. Dearborn St., Chicago 10. Price, $10.00; Canada, $10.50; Foreign, $11.50; individual copy, $1.00.*

A. M. A. Archives of Dermatology. Herbert Rattner, M.D., Chief Editor, 104 S. Michigan Ave., Chicago. Price, $12.00; Canada, $12.50; Foreign, $13.50; individual copy, $1.25.†

A. M. A. Archives of Ophthalmology. Francis Heed Adler, M.D., Chief Editor, 313 S. 17th St., Philadelphia 5. Price, $12.00; Canada, $12.50; Foreign, $13.50; individual copy, $1.25.†

A. M. A. Archives of Surgery. Waltman Walters, M.D., Chief Editor, American Medical Association, 535 N. Dearborn St., Chicago 10. Price, $14.00; Canada, $14.50; Foreign, $15.50; individual copy, $1.25.‡

A. M. A. Journal of Diseases of Children. Robert B. Lawson, M.D., Chief Editor, 1000 N. W. 17th St., Miami 36, Fla. Price, $12.00; Canada, $12.50; Foreign, $13.50; individual copy, $1.25.†

A. M. A. Archives of Pathology. Paul R. Cannon, M.D., Chief Editor, Department of Pathology, University of Chicago, The School of Medicine, 950 E. 59th St., Chicago 37. Price, $10.00; Canada, $10.50; Foreign, $11.50; individual copy, $1.00.*

A. M. A. Archives of Neurology and Psychiatry. Harold G. Wolff, M.D., Chief Editor, Neurology, 525 E. 68th St., New York 21; Roy R. Grinker Sr., M.D., Chief Editor, Psychiatry, Institute for Psychosomatic and Psychiatric Research, 29th St. and Ellis Ave., Chicago 16. Price, $14.00; Canada, $14.50; Foreign, $15.50; individual copy, $1.50.‡

A. M. A. Archives of Otolaryngology. George M. Coates, M.D., Chief Editor, 1721 Pine St., Philadelphia 3. Price, $14.00; Canada, $14.50; Foreign, $15.50; individual copy, $1.50.‡

A. M. A. Archives of Industrial Health. Prof. Philip Drinker, Chief Editor, Dept. of Industrial Hygiene, Harvard University School of Public Health, 55 Shattuck St., Boston 15. Price, $10.00; Canada, $10.50; Foreign, $11.50; individual copy, $1.00.*

* Price to students, interns, and residents: $6.00 in U. S. & possessions.

† Price to students, interns, and residents: $7.00 in U. S. & possessions.

‡ Price to students, interns, and residents: $8.00 in U. S. & possessions.

The price for individual copies applies only to this and the previous calendar year; 5 cents additional is charged for each year preceding the last calendar year.

The Journal of the American Medical Association. Weekly. Annual Subscription Price: Domestic, $15.00. Canadian, $17.00. Foreign, $21.50. Price to students, interns and residents: $9.00 in U. S. & possessions.

Quarterly Cumulative Index Medicus. Issued Twice a Year. Subscription Price, Calendar Year, $25.00.

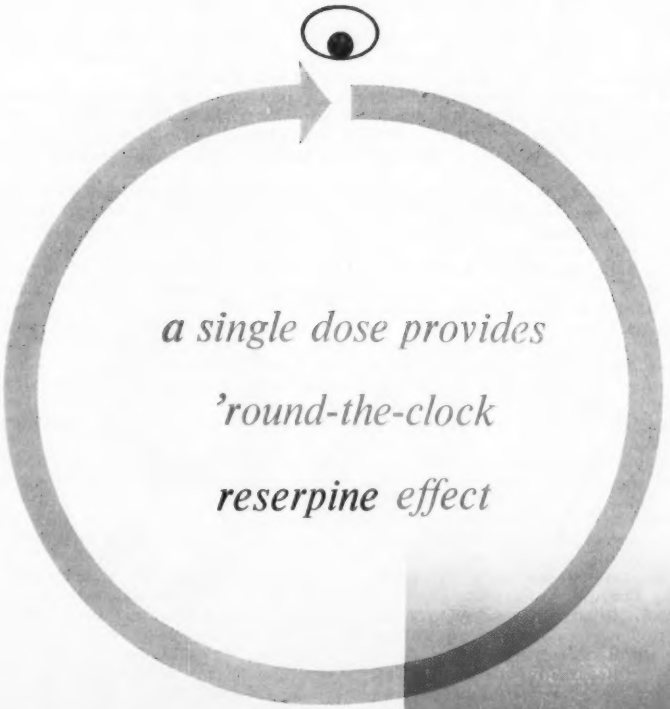
Checks, money orders, and drafts should be made payable to the American Medical Association, 535 North Dearborn Street, Chicago 10.

Published Monthly by

AMERICAN MEDICAL ASSOCIATION

535 NORTH DEARBORN STREET • CHICAGO 10, ILLINOIS

Entered as Second Class Matter Jan. 23, 1909, at the Postoffice at Chicago, Under the Act of March 3, 1879. Annual Subscription, $10.00



a single dose provides

'round-the-clock

***reserpine** effect*

ESKASERP*

reserpine, S.K.F.

SPANSULE†

sustained release capsules, S.K.F.

0.25 mg. *0.50 mg.*

made only by

Smith, Kline & French Laboratories, Philadelphia

first ⧗ in sustained release

oral medication

maximum dosage convenience

for your patients

with hypertension

or requiring a mild,

non-barbiturate sedative

★Trademark
†T.M. Reg. U.S. Pat. Off.
Patent Applied For.

Instructions to Contributors

Communications regarding editorial management, subscriptions, reprints, etc., should be addressed to Specialty Journals, American Medical Association, 535 North Dearborn Street, Chicago 10.

Articles, book reviews, and other materials for publication should be addressed to the Chief Editor of the Specialty Journal concerned. Articles are accepted for publication on condition that they are contributed solely to that journal.

An original typescript of an article should be provided; it must be double or triple spaced on one side of a standard size page, with at least a 1-inch margin at each edge. A carbon copy should be retained by the author. An article in English by a foreign author should be accompanied by a draft in the author's mother tongue. Improvised abbreviations should be avoided.

The main title of an article may not contain more than seventy characters and spaces; a subtitle may be of any length. The subtitle should be sufficiently detached from the main title that a punctuation mark as strong as a colon can be used in the Table of Contents to separate it from the main title; it must not begin with "with."

The author's name should be accompanied by the highest academic or medical degree which he holds. If academic connections are given for one author of an article, such connections must be given for all other authors of the article who have such connections.

A Case Report must be preceded by an introductory paragraph containing at least thirty words before the details of the case are given. To avert the possibility of legal action, patients' initials and hospital case numbers should not be published.

Material quoted from another publication must be quoted exactly if the original is in English—spelling, capitalization, punctuation, etc., unchanged. Material taken largely from another publication must be credited to the original author, whether quoted exactly or merely abstracted.

Each article should be accompanied by a summary in the present tense, presenting the main points of the article, but in somewhat more generalized terms than in the article itself.

If it is necessary to publish a recognizable photograph of a person, the photograph must be accompanied by written permission of the subject himself if an adult, or of the parents or guardian if a child, to publish his photograph. An illustration which has been published in another publication must be accompanied by written permission from the author and the original publisher to reproduce it in an A. M. A. Specialty Journal.

The maximum illustration allowance is ten illustrations within a total of 100 sq. inches or $100, whichever is of greater advantage to the author. When no restrictions are placed by the author upon cropping, reducing, and grouping, the publisher is often able to use twenty or more illustrations in one article with the $100 allowance. See an issue of this journal for examples. Oversized originals should be photographed and a print submitted. Large photomicrograph prints will be reduced in scale unless portions to be cropped are indicated by the author.

Any cut-off marks should be made on the margins (or mountings) rather than on the illustration itself. Charts and drawings should be in black ink on hard, white paper. Lettering must be large enough to permit necessary reduction. Glossy prints of x-rays are requested. Paper clips should not be used on prints, since their mark shows in reproduction, as does writing on the back of prints with hard lead pencil or stiff pen. Labels should be prepared and pasted to the back of each illustration showing its number, the author's name, an abbreviated title of the article, and top plainly indicated. Charts and illustrations must have descriptive legends, grouped on a separate sheet. Tables must have captions. ILLUSTRATIONS SHOULD BE UNMOUNTED.

References to the literature should be numbered in the order in which they are referred to in the text or listed in alphabetical order without numbers. A chronological arrangement, with all entries for a given year alphabetized according to the surname of the first author, may be used if preferred. References should be typed on a special page at end of manuscript. They should conform to the style of the Quarterly Cumulative Index Medicus, and must include, in the order given, name of author, title of article (with subtitle), name of periodical, with volume, page, month—day of month if weekly or biweekly—and year. Names of periodicals should be given in full or abbreviated exactly as in the Quarterly Cumulative Index Medicus. Reference to books must contain, in the order given, name of author, title of book, city of publication, name of publisher, and year of publication. Titles of foreign articles, if originally in a generally known Romance or Germanic tongue, must either all be in English translation or all be in the original language. Titles in other languages must be translated. The author must assume responsibility for the accuracy of foreign titles.

Matter appearing in the A. M. A. Specialty Journals is covered by copyright, but as a rule no objection will be made to its reproduction in a reputable medical journal if proper credit is given. However, the reproduction for commercial purposes of articles appearing in the A. M. A. Specialty Journals, or in any other publications issued by the Association, will not be permitted.

AMERICAN MEDICAL ASSOCIATION

535 North Dearborn Street **Chicago 10**

New, Well Tolerated Medium for Excretory Urography

94%

DIAGNOSTIC FILMS

in a series of 1123 patients

Hypaque® SODIUM
50% solution

Write for detailed literature or consult your local Winthrop representative.

Winthrop LABORATORIES
NEW YORK 18, N.Y. • WINDSOR, ONT.

Hypaque sodium, brand of diatrizoate sodium (sodium 3,5-diacetamido-2,4,6-triiodobenzoate)

an asset to therapeutic diets

Attention to the nutritional requirements of patients effectively supplements medical procedures in helping reduce mortality rates and in shortening convalescence. A state of good nutrition enhances resistance to disease, increases the capacity of tissue for repair, and promotes morale.

Nutritional Advantages

Because of its enrichment and its nonfat milk solids content, the average enriched bread supplies valuable amounts of good quality protein, thiamine, riboflavin, niacin, iron, and calcium. Its protein functions for growth, repair, and maintenance. Its calories help to spare protein for specific protein uses and contribute to energy needs.

The table (right) points up how effectively 6 slices participate in providing good nutrition in illness and convalescence.

Physiologic Advantages

Soft and open in texture, enriched bread is easily masticated and swallowed. It is promptly and thoroughly digested. Its appetizing eating qualities reflexly incite the digestive processes. Producing insignificant amounts of smooth inert residue, it does not irritate the gastric or intestinal mucosa.

Dietetic Advantages

In either fresh or toasted form, enriched bread adds to the eating pleasure of meals. Neutral in flavor, it blends well with other foods. When appetite lags, sandwiches including a wide variety of foods—meat, poultry, eggs, cheese, salad preparations and various spreads—give zest to eating as well as needed nourishment.

These advantages—nutritional, physiologic, and dietetic—establish enriched bread as a valuable asset in therapeutic diets.

Contribution of 6 Slices of Enriched Bread

	Nutrients and Calories	Percentages of Allowances*
Protein	11.7 Gm.	18%
Thiamine	0.33 mg.	22
Niacin	3.0 mg.	20
Riboflavin	0.21 mg.	13
Iron	3.3 mg.	28
Calcium (average)	122 mg.	15
Calories	379	13

*Percentages of daily allowances for 143 lb., 67 in. tall fairly active man of 45. Recommended Dietary Allowances, Washington, D.C., National Academy of Sciences—National Research Council, Publication 302, 1953.

The nutritional statements made in this advertisement have been reviewed and found consistent with current medical opinion by the Council on Foods and Nutrition of the American Medical Association.

AMERICAN BAKERS ASSOCIATION 20 North Wacker Drive • Chicago 6, Illinois

12/15/55 Discharge Note:
This 44-year-old man was admitted on 12/8/55 with a history of fever, back pain and dysuria of three days' duration. Urine culture revealed mixed infection with gram-positive and gram-negative organisms. Diagnosis: pyelonephritis. Oral Terramycin therapy was instituted (2 Gm. the first day, 1 Gm. daily for four days thereafter) in divided doses q. 6 h. Patient was afebrile in 24 hours; culture negative by second day of treatment.

R. Physician, M. D.

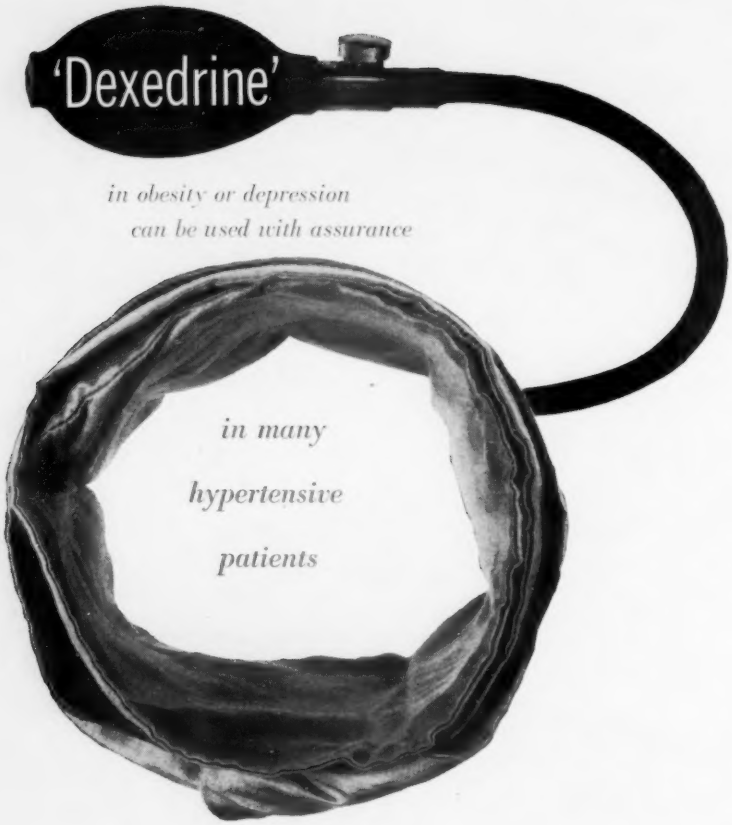
Your histories
are making medical history
in the golden age of antibiotic medicine

TERRAMYCIN

Brand of oxytetracycline

Reports by thousands of physicians on millions of cases have built confidence in Terramycin as a well-tolerated, broad-spectrum antibiotic of choice—now finishing its sixth year of successful clinical use.

Pfizer PFIZER LABORATORIES, *Division, Chas. Pfizer & Co., Inc.*, Brooklyn 6, N. Y.



Dr. Ella Roberts, reporting in Am. Pract. & Dig. Treat. (5:606), states that she administered 'Dexedrine' to 76 patients suffering from hypertension complicated by obesity or depression. Frequent blood pressure readings were made.

At the end of a 2-year study, she concluded:

'Dexedrine' "... is not contraindicated in patients suffering from benign hypertension. ['Dexedrine'] does not bring about a significant or sustained rise in blood pressure when the dose is kept within the normal clinical range (5 to 20 mg. daily)."

Dexedrine* Sulfate **Tablets • Elixir • Spansule† capsules**
dextro-amphetamine sulfate, S.K.F.

made only by

Smith, Kline & French Laboratories, Philadelphia • first ⧗ in sustained release oral medication

*T.M. Reg. U.S. Pat. Off.
†T.M. Reg. U.S. Pat. Off. for sustained release capsules, S.K.F. ° Patent Applied For.

A.M.A. Archives OF
INTERNAL MEDICINE

Aldosterone in Clinical Medicine—Past, Present, and Future

JEROME W. CONN, M.D., Ann Arbor, Mich.

This paper is also appearing this month in the Journal of the Michigan State Medical Society, *a number devoted to honoring the Medical School of the University of Michigan. The* ARCHIVES *is happy to collaborate in this fine gesture to the notable accomplishments of this great medical school.*

Among the outstanding accomplishments of this institution are the studies on aldosterone of Dr. Jerome W. Conn and his associates so modestly reported here.

PAUL S. RHOADS, M.D.

The time has arrived for clinicians to become aware of the increasing importance in clinical medicine of aldosterone, the newly discovered adrenal cortex hormone. It has been demonstrated that increased adrenal production of aldosterone is involved in the pathogenesis of a number of very common clinical disorders. That many more diseases will be found to be associated with increased or decreased secretion of this hormone seems abundantly clear. This prediction is based not only upon the numerous possibilities which exist but also upon the fact that clinical investigators have merely scratched the surface of this fertile field since the hormone was proved to exist and shown to be measurable. A still existent deterrent to rapid progress consists of the very difficult and laborious biological and biochemical procedures which are involved in such studies. Nevertheless, a vista important to all physicians is gradually coming into view.

The purposes of this brief review are (1) to provide that small measure of historical information which is essential for proper orientation to the clinical problems, (2) to delineate and classify the various clinical states in which abnormal production of aldosterone is now known to exist and to speculate upon the existence of others, and (3) to describe in detail primary aldosteronism,* the newly recognized clinical syndrome. Emphasis is given to this condition because it is a serious hypertensive-renal-vascular disease and represents the one condition to date of the entire "aldosterone group" which can be completely cured.

THE DISCOVERY OF ALDOSTERONE

The history of aldosterone is still in the making. It goes back only to 1952, when Simpson, Tait, and their co-workers † detected biologically, and isolated chromatographically, from the "amorphous fraction" ‡ of adrenal cortex extract something which caused intense retention of sodium and diuresis of potassium in adrenalectomized

Submitted for publication Dec. 2, 1955.

Professor of Internal Medicine, Director of the Division of Endocrinology and Metabolism and the Metabolism Research Unit, Department of Internal Medicine, University of Michigan Medical School.

* References 1 and 2.

† References 4-7.

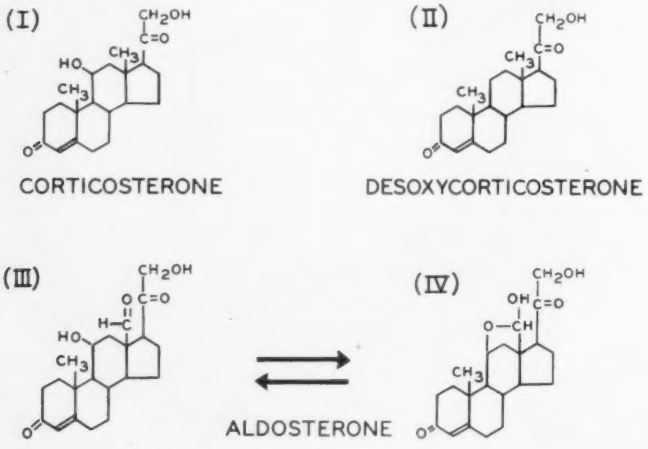
‡ The noncrystalline residue which remains after the known crystalline steroids have been removed. This residue has been known for many years to have high biological activity when tested on adrenalectomized animals.

rats. The potency of this material was so great that these investigators realized at once that they were not dealing with any of the known corticosteroids or with any combination of them. They [8] and Farrell and Richards [9] demonstrated the existence of this material in the adrenal venous blood of monkeys and dogs. This constituted good evidence that this substance was a normal secretory product of the adrenal gland. Because of its potent effect upon electrolyte metabolism (30 times greater on sodium retention and 5 times greater on potassium

It is important to realize that much basic work on the "amorphous fraction" of adrenal extract had already been done ¶ and that the stage had been set for the brilliant discoveries of the 1952-1955 era.#

THE CLINICAL BACKGROUND

From the clinical point of view, too, it had been suspected that the adrenal was capable of secreting a powerful electrolyte-regulating hormone, although it was assumed by many, without proper justification, that this steroid was probably desoxy-



NATURAL COMPOUNDS EXHIBITING A PREPONDERANT ACTIVITY UPON ELECTROLYTE METABOLISM

diuresis than desoxycorticosterone) the material was tentatively given the name "electrocortin."

There then ensued, in relatively rapid succession, isolation of the compound in pure crystalline form,§ identification of its chemical structure,‖ and, in July, 1955, actual synthesis of the compound.[16] In the accompanying Figure, (*III*) indicates the chemical formula of aldosterone, the 18-aldehyde of corticosterone (*I*). In solution, a major portion of aldosterone exists as the hemiacetal, Figure, (*IV*). Desoxycorticosterone is shown, too (Fig. [*II*]).

corticosterone. The latter has been used to regulate electrolyte metabolism in patients with Addison's disease since Steiger and Reichstein [21] synthesized the compound, in 1937. When cortisone and hydrocortisone became available for substitution therapy in Addison's disease it was quickly apparent that doses of these compounds adequate to normalize organic metabolism (protein, carbohydrate, etc.) lacked the capacity to maintain normal metabolism of sodium and potassium. It was found necessary to give these patients desoxycorticosterone in addition to maintenance quantities of cortisone or hydro-

§ References 10-12.

‖ References 13-15.

¶ References 17-20.

Many investigations which contributed directly or indirectly to this background have been omitted.

cortisone. Corticosterone, Figure, (*I*), however, was found to provide, in a single compound, good replacement therapy.[22]

In 1950 Deming and Luetscher [23] reported the presence of a sodium-retaining substance in urine of edematous patients with nephrosis and cardiac disease. Luetscher and his co-workers * have continued to work diligently on this important problem and have culminated their studies with the recent demonstration [31] that the urinary sodium-retaining substance is, indeed, aldosterone.

In a series of reports which began in 1944, my associates and I † demonstrated that the concentrations of sodium and chloride of thermal sweat could be used as an index of the activity of endogenously produced "desoxycorticosterone-like" or "salt-active" corticosteroids. Using this index, we made the following observations:

1. Under conditions of sodium deprivation in man (prolonged sweating and low-sodium diets) the adrenals are capable of maintaining an excessive output of desoxycorticosterone-like steroids for long periods of time (months), and this activity is not accompanied by any evidence of increased production of other types of adrenal steroids.‡ These experiments were repeated recently,[38] this time with use of the newer urinary bioassay techniques. It was found that the "desoxycorticosterone-like" steroid produced in excess is aldosterone, indeed. Axelrad and co-workers [39] have shown recently that severe restriction of dietary sodium leads to increased production of aldosterone, unaccompanied by evidence of increased secretion of other adrenal cortex hormones.

2. Again, with the electrolyte composition of sweat used as the index,[36] patients with panhypopituitarism were found to be producing almost normal quantities of the desoxycorticosterone-like steroids, while patients with Addison's disease produced much less, if any. Luetscher [28] has shown recently that this relationship is true with respect to urinary aldosterone in these respective groups of patients.

3. Patients with Cushing's syndrome due to bilateral adrenal cortex hyperplasia showed only mild increases in production of desoxycorticosterone-like steroids, while two patients with adrenal cortex cancer (one with Cushing's syndrome and one with adrenogenital syndrome) indicated the production of greatly excessive amounts of salt-active corticoids.[36] Venning and co-workers [40] have reported recently that Cushing's syndrome associated with adrenal cancer gives large amounts of urinary aldosterone, while that associated with hyperplasia shows no demonstrable increase.

4. Following surgical operations the sweat-electrolyte index gave evidence of a greatly increased production of desoxycorticosterone-like steroids, which continued for a considerable length of time in the postoperative period.[41] That aldosterone production is increased at this time has now been demonstrated by Llaurado § and by Venning and co-workers.[40]

5. The following statement was made in 1949 [36]: "It is predicted that some pathological conditions not yet linked to the adrenal cortex, as well as the physiologic response to some forms of stress, will be found to be associated with a preponderant activity of the desoxy-like corticosteroids." These authors [37] singled out nephrosis, congestive heart failure, premenstrual edema, and essential hypertension as diseases worthy of study in this regard, but they stated [36] that "notable anasarca need not be an accompaniment of excessive production of desoxy-like corticosteroids." The recent discovery of the syndrome of primary aldosteronism [1] and the demonstration that an assortment of common clinical diseases exhibit excessive production of aldosterone have confirmed their suspicions.

PRESENT STATUS OF ALDOSTERONE IN CLINICAL MEDICINE

The Table presents a tentative etiological classification of hyperaldosteronism and

* References 24-30.

† References 32-38.

‡ References 35 and 37.

§ References 42 and 43.

Etiological Classification of Conditions Associated with Excessive or Diminished Production of Aldosterone *

I. Hyperaldosteronism

A. Primary aldosteronism

1. "Pure type" (normal production of hydrocortisone)
   (*a*) Adrenal cortex adenoma †
   (*b*) Bilateral adrenal cortex hyperplasia
   (*c*) Adrenal cortex carcinoma (not yet reported) *

2. "Mixed types" (excessive production of hydrocortisone, too)
   (*a*) Adrenal cortex carcinoma [40]
   (*b*) Adrenal metastases from bronchogenic carcinoma §
   (*c*) Others will be described *

B. Secondary aldosteronism

1. With edema (normal production of hydrocortisone)
   (*a*) Nephrosis [31]
   (*b*) Congestive cardiac failure [29]
   (*c*) Cirrhosis of the liver ‖
   (*d*) Eclampsia [45]
   (*e*) Idiopathic edema [60]
   (*f*) Others will be described *

2. Without edema (normal production of hydrocortisone)
   (*a*) "Salt-losing nephritis" [59]
   (*b*) Dietary restriction of sodium [39]
   (*c*) Intense sweating [38]
   (*d*) Others will be described *

3. Transient aldosteronism (increased production of hydrocortisone)
   (*a*) Following surgical trauma ¶
   (*b*) Others will be described with other situations which induce "stress" *

II. Hypoaldosteronism

A. Primary aldosteronopenia

1. "Pure type" (normal production of hydrocortisone) (not yet described) *

2. "Mixed type" (diminished production of hydrocortisone, too)
   (*a*) Addison's disease [28]
      (1) Bilateral destructive lesions of adrenal cortices
      (2) Idiopathic (primary) cortical atrophy
   (*b*) ? Congenital adrenal hyperplasia with excessive renal loss of sodium *

B. Secondary aldosteronopenia *

1. Transient—probably exists after removal of an aldosteronoma as well as under other circumstances

2. Chronic—not yet described; must await clarification of the physiological mechanisms which stimulate and depress secretion of aldosterone

* The asterisk indicates that I expect more information to develop at these points in the classification.
† References 1, 2, and 46.
§ Reference 55; Gordon, E. S.: Personal communication to the author.
‖ References 26 and 58.
¶ References 40-43.

hypoaldosteronism. Included are the clinical conditions now known to be associated with abnormal production of aldosterone. In addition, it will be noted that names have been given to conditions which are not yet recognized as existing. We believe that many of them will be found to occur.

Hyperaldosteronism is divided into two main subgroups, primary aldosteronism and secondary aldosteronism. The former is meant to denote an abnormality of the adrenal cortex which, per se, gives rise to secretion of excessive amounts of aldosterone. Secondary aldosteronism indicates a situation in which excessive production of aldosterone is the result of an abnormality which has arisen outside of the adrenal gland. The adrenal then responds normally to an intense physiological stimulus or stimuli capable of evoking increased secretion of

aldosterone. Secondary hormonal secretory activities of this nature are usually compensatory and are designed to overcome or buffer a biochemical abnormality which has arisen.

A similar division into subgroups has been assigned to hypoaldosteronism, primary aldosteronopenia indicating an abnormality of the adrenal itself and secondary aldosteronopenia representing a compensatory reduction of aldosterone production based upon an extra-adrenal abnormality.

Secondary Aldosteronism and Secondary Aldosteronopenia

The physiological mechanisms which increase and decrease adrenal secretion of aldosterone from the normal gland remain unknown at present. Thus, the precise stimuli, biochemical or physiological, which increase production of aldosterone in those diseases (nephrosis, congestive heart failure, hepatic cirrhosis, eclampsia, idiopathic edema) associated with secondary aldosteronism are yet to be discovered. The answers are being sought diligently in many laboratories, for they will provide insight into the mechanisms of a large number of disturbances in electrolyte metabolism. The same statements apply to the projected group of disturbances which have been classified under the heading of secondary aldosteronopenia.

Since little is known, in a positive sense, of the mechanisms which control secretion of aldosterone from normal adrenal glands, there is at present no direct approach to the medical management of secondary aldosteronism. Obviously, bilateral adrenalectomy would remove the source of aldosterone in cases of intractable edema associated with secondary aldosteronism. But there is no justification as yet for this procedure. If the secondary increase in aldosterone production proves to be compensatory, representing an attempt to normalize a presently undiscovered biochemical abnormality, the result may prove more deleterious than the persistence of edema. A rough analogy is seen in the diabetic under conditions of stress (surgery, injury, infections, etc.). Stress produces in him, as in all people, secondary hydrocortisonism. The latter is necessary if he is to survive the stressful experience. The increase of hydrocortisone, however, may cause great insulin resistance and an intense exacerbation of his hyperglycemia and glycosuria. Adrenalectomy can ameliorate diabetes mellitius, but the associated consequences must be weighed against the apparent benefit to the diabetic state.

Administration of corticotropin (ACTH) or cortisone to edematous nephrotics is frequently successful in producing great diuresis and, in fact, is capable of reducing urinary excretion of aldosterone.[24] How this comes about is unknown, but a possible mechanism has been suggested.[1] A point of considerable interest and importance is the fact that aldosterone secretion is not predominantly controlled by pituitary corticotropin, as are the other major products of the adrenal cortex. Hypophysectomy in the dog results in but a moderate decrease in the level of aldosterone in adrenal venous blood.[44] The level of hydrocortisone, however, falls abruptly and to negligible amounts. Normal levels of urinary aldosterone are found in patients with hypopituitarism at a time when they exhibit greatly decreased amounts of urinary 17-hydroxycorticoids and 17-ketosteroids.[28] Conditions can be arranged, such as deprivation of sodium chloride and severe, prolonged sweating, in which one can demonstrate a tremendous increase of urinary aldosterone, unaccompanied by any other evidence of increased adrenal cortex activity.[38] Administration of corticotropin to man results in only minor elevation of urinary aldosterone as compared with the major increase that occurs with respect to 17-hydroxycorticoid.‖ Thus, the adrenal gland has the capacity to increase its output of aldosterone selectively. The mechanism by which this is brought about does not involve stimulation of the gland by corticotropin; at least, not by the compound that we now recognize as corticotropin. However, any stimulus which enhances adrenal secretion

‖ References 39 and 45.

of aldosterone would also have to be considered as an adrenocorticotropic factor. Whether or not this factor is hormonal in nature must await further work. Since hypophysectomy produces only a minor decrease in the secretion of aldosterone, a nonpituitary stimulator must be involved. Changes in extracellular fluid volume, changes in plasma and tissue electrolyte concentrations, and changes in renal dynamics are probably involved in the regulation of aldosterone secretion. Since nothing more is known, this is the point at which the clinical syndromes associated with secondary aldosteronism must be left at present.

Primary Aldosteronism

Primary aldosteronism is the one condition in the group of disturbances of aldosterone secretion which can be cured. The cause is an aldosterone-secreting adrenal cortex adenoma. Its clinical recognition is not difficult.

The syndrome was first described in October, 1954.¶ Since then a surprisingly large number of typical cases (at least 30) have been recognized clinically as being instances of primary aldosteronism,# and some of these patients are being readied for adrenal surgery. To date, we are aware of 10 patients, including the original case,[2] who have had the typical clinical findings and in whom an adrenal cortex tumor has been demonstrated.* In 6 of the 10 cases determinations were made for urinary aldosterone.† In all 6 very large amounts were shown to be present. An 11th case is said to have shown bilateral cortical hyperplasia and to have been cured by bilateral adrenalectomy. Three more cases have been recognized in retrospect, each having disclosed a single cortical adenoma at autopsy and each having suffered during life from primary aldosteronism.§ The rapidity with which so many cases have been recognized following the original description of the syndrome suggests that this is not a rare disease.

The major clinical manifestations of this syndrome consist of periodic severe muscular weakness, intermittent tetany and paresthesia, polyuria and polydipsia, and hypertension. There is no edema; nor is there any evidence of Cushing's syndrome.

The characteristic biochemical lesion in blood is comprised of hypokalemia, hypernatremia, and alkalosis (elevation of pH and CO_2-combining power). Total serum calcium is normal. Hyposthenuria, unresponsive to vasopressin (Pitressin), persistently alkaline urine, and mild proteinuria are observed. Bioassays for urinary aldosterone give extremely high values, while urinary 17-hydroxycorticoids and 17-ketosteroids remain persistently normal.

Despite the periodic occurrence of severe muscular weakness, one is impressed with the relative lack of important symptoms at extremely low levels of serum potassium. Another striking manifestation of this syndrome is the great resistance which it offers against attempts at potassium repletion. With very large amounts of supplementary potassium, serum potassium rises, but only mildly. It seems certain that the condition which descriptively has been called "potassium-losing nephritis" ‖ is a manifestation of primary aldosteronism.

In the investigative laboratory the following findings, too, have been demonstrated ¶:

1. The concentrations of sodium and chloride of sweat and saliva are greatly depressed, while that of potassium is abnor-

¶ References 1 and 2.

Personal communications to the author.

* References 46 and 47. Crane, M. G., Los Angeles, two proved cases, to be published; Bartter, F. C., Bethesda, Md.; Hewlett, J., Cleveland Clinic, three proved cases, to be published; Milne, M.D., London, England; Earles, L., Capetown, South Africa: Personal communications to the author.

† Reference 46. Hewlett, J.: Personal communication to the author; Milne, M. D.: Personal communication to the author; Crane, M. G.: Personal communication to the author.

§ Keutman, E. H., Rochester, N. Y.; Steinbeck, A. W., Brisbane, Australia; Meiselas, L. E., Brooklyn: Personal communications to the author.

‖ References 49-53.

¶ References 1, 2, and 46.

mally high. This indicates intense biological activity of a sodium-retaining corticoid.

2. There exists negative balance for potassium in the presence of sodium equilibrium and of nitrogen equilibrium.

3. The biochemical lesion is confined to electrolyte metabolism, organic metabolism being normal.

4. Analyses of large-muscle biopsies demonstrate a great excess of intracellular sodium and a great deficiency of intracellular potassium.

5. Bioassay for aldosterone in the cortical tumor tissue gave values (on a per gram basis) many times greater than that found in beef or hog adrenal; also, 30 times greater than that found in an adrenal tumor that had produced Cushing's syndrome. Paper chromatographic study of extracts of the tumor reveals the active material to be aldosterone.

6. Biopsies of both kidneys reveal a diffuse vacuolar nephropathy, the so-called "clear-cell nephrosis," which is characteristic of chronic hypokalemia. This is the cause of the hyposthenuria.[54] Severe renal arteriolosclerosis is also found.

7. Disappearance of the entire clinical and biochemical abnormality (hypertension included) is complete within two weeks following removal of the cortical adenoma.

It is recommended that patients exhibiting the clinical and biochemical abnormalities described above be subjected to adrenal surgery. It is likely, from the information available to date, that the great majority of such patients harbor an adrenal cortex tumor producing excessive amounts of aldosterone (aldosteronoma). However, there is reason to believe that in some patients with this syndrome a tumor will not be found at operation.# Under these circumstances a total adrenalectomy (or an extensive subtotal one, pending future experience) should be performed.

As indicated in the classification (Table), an element of primary aldosteronism may exist in association with excessive production of other adrenal corticoids, particularly in malignancies involving the adrenal gland.* However, in such cases, the clinical picture produced by the other corticoids, as well as the presence of excessive amounts of other excretory steroids in the urine, focuses one's attention upon the adrenal as the source of the difficulty.

In "pure" primary aldosteronism such tell-tale signs pointing to adrenal involvement are absent, since urinary 17-ketosteroids and 17-hydroxycorticoids are normal. The clinical picture and the biochemical lesion as described above, however, are characteristic and should now suggest to the physician that he is dealing with an abnormality of adrenal cortex function.

Primary Aldosteronopenia

A situation has not yet been described in which there is primary adrenal failure to produce sufficient aldosterone in association with a maintained capacity to secrete normal quantities of the other corticoids. It is possible, however, that it exists. Since, on the basis of present knowledge, a diminished concentration of aldosterone in blood would not be expected to activate increased secretion of corticotropin (as a diminshed blood level of hydrocortisone is known to do), there would occur no increase in urinary steroid excretion (17-hydroxysteroids and 17-ketosteroids) to suggest an adrenal etiology for such a condition. Better quantitative methods for determination of aldosterone in blood will have to be devised before this postulated condition can be sought.

It is clear to those familiar with this field that an analogy has been drawn above with the condition now known as congenital adrenal hyperplasia (see Table). The latter condition is one in which a primary adrenal defect exists with respect to the steroidogenesis of hydrocortisone. According to the terminology used in our classification, the name "primary hydrocortisonopenia" would describe the situation better than the one now in use. In any case, the low level of

Reference 52.

* References 40 and 55; Gordon, E. S.: Personal communication to the author.

blood hydrocortisone results in increased release of corticotropin, which, in turn, produces bilateral cortical hyperplasia and greatly increased production of those steroids (mainly androgenic ones) in which no defect in steroidogenesis exists. Thus, the clinical result of "primary hydrocortisonopenia" is virilization, the so-called adrenogenital syndrome.

Many of these patients (primary hydrocortisonopenia) demonstrate a defect of electrolyte metabolism similar in all respects to that seen in Addison's disease. This is correctable, as in the Addisonian, by administration of desoxycorticosterone. This suggests that, in addition to primary hydrocortisonopenia, a variable degree of primary aldosteronopenia may exist as well. Hypothetically, the pathway for steroidogenesis of aldosterone is similar to that of corticosterone.† It is possible, therefore, that the same enzymatic defect which interferes with normal syntheses of hydrocortisone results also in decreased production of aldosterone. But another possibility exists. Sodium loss in such patients could prove to be due to the presence of a substance which actively inhibits renal tubular reabsorption of sodium. Under such conditions, production of aldosterone, if intact, would actually increase above normal. With respect to aldosterone, the condition would then have to be included as one of secondary aldosteronism. Leutscher [59] has, in fact, reported an abnormally high quantity of sodium-retaining steroid in the urine of a patient with the salt-losing type of congenital adrenal hyperplasia. In the Table, a (?) is placed before congenital adrenal hyperplasia, pending future clarification of these possibilities.

That primary aldosteronopenia exists in Addison's disease along with deficiency of all other adrenal secretory products goes without saying. It is placed in the classification for the sake of completeness. It is likely that, with the recent synthesis of aldosterone,[16] this compound will soon be available for use as physiological replacement therapy. It is effective when given orally. In proper combination with hydrocortisone it constitutes future natural replacement treatment of Addison's disease.

† References 56 and 57.

REFERENCES

1. Conn, J. W.: Primary Aldosteronism: A New Clinical Syndrome, J. Lab. & Clin. Med. **45**:6, 1955.

2. Conn, J. W.: Primary Aldosteronism: Progress Report, J. Lab. & Clin. Med. **45**:661, 1955.

3. Simpson, S. A., and Tait, J. F.: A Quantitative Method for the Bioassay of the Effect of Adrenal Cortical Steroids on Mineral Metabolism, Endocrinology **50**:150, 1952.

4. Tait, J. F.; Simpson, S. A., and Grundy, H. M.: The Effect of Adrenal Extract on Mineral Metabolism, Lancet **1**:122, 1952.

5. Grundy, H. M.; Simpson, S. A., and Tait, J. F.: Isolation of a Highly Active Mineralocorticoid from Beef Adrenal Extract, Nature, London **169**:795, 1952.

6. Grundy, H. M.; Simpson, S. A.; Tait, J. F., and Woodford, M.: Further Studies on the Properties of a Highly Active Mineralocorticoid, Acta endocrinol. **11**:119, 1952.

7. Simpson, S. A., and Tait, J. F.: Physioco-Chemical Methods of Detection of a Previously Unidentified Adrenal Hormone, in Memoirs of the Society for Endocrinology, London, No. 2, November, 1953.

8. Simpson, S. A.; Tait, J. F., and Bush, I. E.: Secretion of a Salt-Retaining Hormone by the Mammalian Adrenal Cortex, Lancet **2**:226, 1952.

9. Farrell, G. L., and Richards, J. B.: Isolation of a Potent Sodium-Retaining Substance from Adrenal Venous Blood of the Dog, Proc. Soc. Exper. Biol. & Med. **83**:628, 1953.

10. Simpson, S. A.; Tait, J. F.; Wettstein, A.; Neher, R.; Euw, J. V., and Reichstein, T.: Isolierung eines neuen kristallisierten Hormons aus Nebennieren mit besonders hoher Wirksamkeit auf den Mineralstoffwechsel, Experientia **9**:333, 1953.

11. Mattox, V. R.; Mason, H. L., and Albert, A.: Isolation of a Sodium-Retaining Substance from Beef Adrenal Extracts, Proc. Staff Meet. Mayo Clin. **28**:596, 1953.

12. Mattox, V. R.; Mason, H. L.; Albert, A., and Code, C. F.: Properties of a Sodium-Retaining Substance from Adrenal Extract, J. Am. Chem. Soc. **75**:4869, 1953.

13. Simpson, S. A.; Tait, J. F.; Wettstein, A.; Neher, R.; Euw, J. V.; Schindler, O., and Reichstein, T.: Konstitution des Aldosterons, des neuen Mineralocorticoids, Experientia **10**:132, 1954.

14. Simpson, S. A.; Tait, J. F.; Wettstein, A.; Neher, R.; Euw, J. V.; Schindler, O., and Reichstein, T.: Aldosteron: Isolierung und Eigenschaften; Über Bestandteile der Nebennierenrinde und verwandte Stoffe, Helvet. chim. acta **37**:1163, 1954.

15. Simpson, S. A.; Tait, J. F.; Wettstein, A.; Neher, R.; Euw, J. V.; Schindler, O., and Reichstein, T.: Die Konstitution des Aldosterons: Über Bestandteile der Nebennierenrinde und verwandte Stoffe, Helvet. chim. acta **37**:1200, 1954.

16. Wettstein, A., and others, Synthesis of Aldosterone, read before the International Congress of Pure and Applied Chemistry, Zurich, Switzerland, July 22, 1955.

17. Pfiffner, J. J.; Wintersteiner, O., and Vass, H. M.: Chemical Studies on the Adrenal Cortex: I. Fractionation Studies on Hormone Concentrates, J. Biol. Chem. **111**:585, 1935.

18. Wintersteiner, O., and Pfiffner, J. J.: Chemical Studies on the Adrenal Cortex: III. Isolation of 2 Physiologically Inactive Compounds, J. Biol. Chem. **116**:291, 1936.

19. Mason, H. L.: Chemistry of the Adrenal Cortical Hormone, Endocrinology **25**:405, 1939.

20. Kendall, E. C.: Glandular Physiology and Therapy: The Function of the Adrenal Cortex, J. A. M. A. **116**:2394, 1941.

21. Steiger, M., and Reichstein, T.: Desoxycorti-steron (21-Oxy-progesteron) aus Δ^5-3-Oxyatio-cholensäure, Helvet. chim. acta **20**:1164, 1937.

22. Conn, J. W.; Fajans, S. S., and Louis, L. H.: Metabolic Effects in Man of Orally and Parenterally Administered Corticosterone (Compound B), Tr. A. Am. Physicians **64**:269, 1951.

23. Deming, Q. B., and Luetscher, J. A., Jr.: Bioassay of Desoxycorticosterone-like Material in Urine, Proc. Soc. Exper. Biol. & Med. **73**:171, 1950.

24. Luetscher, J. A., Jr.; Deming, Q. B., and Johnson, B. B.: Treatment of Nephrosis with Pituitary Adrenocorticotropin, J. Clin. Invest. **30**:1530, 1951.

25. Luetscher, J. A., Jr.; Deming, Q. B., and Johnson, B. B.: The Sodium-Retaining Activity of the Corticoid Fraction of Urine of Oedematous Patients, in Ciba Foundation Colloquia on Endocrinology: Vol. IV. Anterior Pituitary Secretion and Hormonal Influences in Water Metabolism, edited by G. E. W. Wolstenholme and M. Cameron, New York, The Blakiston Company, 1952, p. 530.

26. Luetscher, J. A., Jr., in Symposium on Adrenal Function of Infants and Children, State University of New York, Syracuse, N. Y., Nov., 1954, p. 57.

27. Luetscher, J. A., Jr.: Chromatographic Separation of the Sodium-Retaining Corticoid from the Urine of Children with Nephrosis, Compared with Observations on Normal Children, J. Clin. Invest. **33**:276, 1954.

28. Luetscher, J. A., Jr., and Axelrad, B. J.: Sodium-Retaining Corticoid in the Urine of Normal Children and Adults and of Patients with Hypoadrenalism or Hypopituitarism, J. Clin. Endocrinol. **14**:1086, 1954.

29. Luetscher, J. A., Jr., and Johnson, B. B.: Observations on the Sodium-Retaining Corticoid (Aldosterone) in the Urine of Children and Adults in Relation to Sodium Balance and Oedema, J. Clin. Invest. **23**:1441, 1954.

30. Luetscher, J. A., Jr.; Johnson, B. B.; Axelrad, B. J.; Cates, J. E., and Sala, G.: Apparent Identity of Electrocortin with Sodium-Retaining Corticoid Extracted from Human Urine, J. Clin. Endocrinol. **14**:812, 1954.

31. Luetscher, J. A., Jr.; Neher, R., and Wettstein, A.: Isolation of Crystalline Aldosterone from the Urine of a Nephrotic Patient, Experientia **10**: 456, 1954.

32. Conn, J. W., and Johnston, M. W.: The Function of the Sweat Glands in the Economy of NaCl Under Conditions of Hard Work in a Tropical Climate, J. Clin. Invest. **23**:933, 1944.

33. Conn, J. W.; Johnston, M. W., and Louis, L. H.: Acclimatization to Humid Heat: A Function of Adrenal Cortical Activity, J. Clin. Invest. **25**:912, 1946.

34. Conn, J. W.; Louis, L. H.; Johnston, M. W., and Johnson, B.: The Electrolyte Content of Thermal Sweat as an Index of Adrenal Cortical Function, J. Clin. Invest. **27**:529, 1948.

35. Conn, J. W.: The Mechanism of Acclimatization to Heat, in Advances in Internal Medicine, New York, Interscience Publishers, Inc., 1949, Vol. 3, pp. 373-393.

36. Conn, J. W.: Electrolyte Composition of Sweat: Clinical Implications as an Index of Adrenal Cortical Function, Arch. Int. Med. **83**:416, 1949.

37. Conn, J. W., and Louis, L. H.: Production of Endogenous Salt-Active Corticoids as Reflected in the Concentrations of Sodium and Chloride of Thermal Sweat, J. Clin. Endocrinol. **10**:12, 1950.

38. Streeten, D. H. P.; Conn, J. W.; Louis, L. H.; Fajans, S. S.; Seltzer, H. S.; Johnson, R. D.; Gittler, R. D., and Dube, A. H.: Secondary Aldosteronism: I. The Metabolic and Adrenocortical Responses of Normal Men to High Environmental Temperatures, J. Lab. & Clin. Med., to be published.

39. Axelrad, B. J.; Johnson, B. B., and Luetscher, J. A., Jr.: Factors Regulating the Output of Sodium-Retaining Corticoid of Human Urine, J. Clin. Endocrinol. **14**:783, 1954.

40. Venning, E. G.; Carballeira, A., and Dyrenfurth, I.: Excretion of Sodium-Retaining Substances, J. Clin. Endocrinol. **14**:784, 1954.

41. Johnson, H. T.; Conn, J. W.; Iob, V., and Coller, F. A.: Postoperative Salt Retention and Its Relation to Increased Adrenal Cortical Function, Ann. Surg. **132**:374, 1950.

42. Llaurado, J. G.: Sodium-Potassium Ratio and Excretion of Aldosterone in Urine of Patients Following Surgical Trauma, Proc. Univ. Otago Med. School (New Zealand) **32**:20, 1954.

43. Llaurado, J. G.: Studies on the Excretion of Aldosterone Following Surgical Trauma: Transient Aldosteronism, Proc. Univ. Otago Medical School (New Zealand) **33**:19, 1955.

44. Farrell, G. L.; Royce, P. C.; Rauschkolb, E. W., and Hirschmann, H.: Isolation and Identification of Aldosterone from Adrenal Venous Blood, Proc. Soc. Exper. Biol. & Med. **87**:141, 1954.

45. Gordon, E. S.; Chart, J. J.; Hagedorn, D., and Shipley, E. G.: Mechanism of Sodium Retention in Preeclamptic Toxemia, Obst. & Gynec. **4**: 39, 1954.

46. Conn, J. W., and Louis, L. H.: Primary Aldosteronism, Tr. A. Am. Physicians **68**:215, 1955.

47. Mader, I. J., and Iseri, L. T.: Spontaneous Hypopotassemia, Hypomagnesemia, Alkalosis and Tetany Due to Hypersecretion of Corticosterone-like Mineralocorticoid, Am. J. Med. **19**:976, 1955.

48. Reference deleted.

49. Conn, J. W.: Potassium-Losing Nephritis, Brit. M. J. **2**:1414, 1954.

50. Evans, B. M., and Milne, M. D.: Potassium-Losing Nephritis Presenting as a Case of Periodic Paralysis, Brit. M. J. **2**:1067, 1954.

51. Cope, C. L., and Milne, M. D.: Primary Aldosteronism, Brit. M. J. **1**:969, 1955.

52. Wyngaarden, J. B.; Keitel, H. G., and Isselbacker, J.: Potassium Depletion and Alkalosis: Their Association with Hypertension and Renal Insufficiency, New England J. Med. **250**:597, 1954.

53. Earl, D. P.; Sherry, S.; Eichna, L. W., and Conan, N. J.: Low Potassium Syndrome Due to Defective Renal Tubular Mechanism for Handling Potassium, Am. J. Med. **11**:283, 1951.

54. Schwartz, W. B., and Relman, A. S.: Metabolic and Retinal Studies in Chronic Potassium-Depletion Resulting from Overuse of Laxatives, J. Clin. Invest. **32**:258, 1953.

55. Spaulding, W. P.; Qille, W. A., and Gornall, A. G.: Mineralocorticoid-like Disturbance Associated with Adrenal Metastases from a Bronchogenic Carcinoma, Ann. Int. Med. **42**:444, 1955.

56. Hector, O., and Pincus, G.: Genesis of Adrenocortical Secretion, Physiol. Rev. **34**:459, 1954.

57. Pincus, G.: The Biosynthesis of Adrenal Steroids, Ann. New York Acad. Sc. **61**:283, 1955.

58. Pechet, M. M.; Duncan, L. E., Jr.; Liddle, G. W., and Bartter, F. C.: Studies on a Salt Retaining Factor Prepared from Human Urine, J. Clin. Invest. **33**:957, 1954.

59. Luetscher, J. A., Jr., and Curtis, R. H.: Relationship of Aldosterone in Urine to Sodium Balance and to Some Other Endocrine Functions, J. Clin. Invest. **34**:951, 1955.

60. Mach, R.; Fabre, J.; Muller, A.; Neher, R., and Borth, R.: Oedéma idiopathique par retention sodique avec hyperaldostéronurie, Bull. et mem. soc. med. Hóp. Paris **71**:726, 1955.

Studies on the Destruction of Red Blood Cells

X. The Biophysics and Biology of Sickle-Cell Disease

JOHN W. HARRIS, M.D.
HENRY H. BREWSTER, M.D.
THOMAS HALE HAM, M.D., Cleveland
and
WILLIAM B. CASTLE, M.D., Boston

In 1927, in a classic paper, Hahn and Gillespie [19] clearly defined the basis of the anomalous physical behavior of the sickle cell as an abnormality of its hemoglobin when in the deoxygenated state and pointed to the affected cells as the primary cause of the characteristic hemolytic anemia. From microscopic observations of drops of blood suspended in a gas chamber and from the results of the removal of a large spleen from a child with sicklemia, they were led to make the following statement:

> Sickle cell formation is a reversible phenomenon depending on the free or combined state of the hemoglobin of the susceptible corpuscles. When the hemoglobin is in the combined state, the discoid form is stable; when in the uncombined state, the distorted form is stable. The behavior of the susceptible corpuscles toward oxygen asphyxia thus constitutes a special application of a hypothesis correlating contour with the state of the hemoglobin. . . . The failure of corpuscles which have lost their hemoglobin to undergo sickle cell formation is consistent with our hypothesis relating the distortion to the hemoglobin. . . . It is reasonable to suppose that sickle cells are formed in the body of an affected person wherever the oxygen tension and hydrogen ion concentration are such as to render the distorted form of the corpuscles stable. . . . We are not inclined to evoke the questionable hypothesis of "hypersplenism." . . . It is enough to assume that the spleen merely performs its usual function in sickle cell anemia, that of capturing and destroying damaged or abnormal red blood corpuscles, and that in performing this office, it is damaged itself.

Hahn and Gillespie also observed that sickling began when the oxygen tension of a drop of blood was reduced to about 45 mm. of mercury, provided the pH of the blood was below 7.4, and thus related the sickling prenomenon to the oxygen dissociation curve of hemoglobin. Three years later Scriver and Waugh [20] confirmed the physiologic significance of these variables with samples of venous blood drawn under oil from a child with severe sickle-cell anemia. More sickled cells and carbon dioxide but less oxygen were found in samples obtained during venous stasis of an extremity. In this way the influence upon the sickling phenomenon of the local tissue oxygen consumption and carbon dioxide production were demonstrated in the living patient.

In 1940 the finding that it was impossible to reduce the apparent hematocrit value of deoxygenated portions of sickle-cell blood to that of oxygenated portions of the same sample even by prolonged centrifugation led to an investigation of the effect of deoxygenation upon the viscosity of sickle-cell blood. It was shown [28] that when the oxygen tension of sickle-cell blood was reduced to 40 mm. or less the time required for samples of it to pass through an Ostwald viscometer became significantly increased. With com-

Submitted for publication Sept. 30, 1955.

This is one of a series of three articles concerning the hemolytic anemias, appearing in the A. M. A. Archives of Internal Medicine.

Supported in part by The John and Mary R. Markle Foundation and the Medical Division of the Atomic Energy Commission, Contract No. AT (30-1)-675.

From the Thorndike Memorial Laboratory, The Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School. Research Fellow of the American College of Physicians for 1951-1952, present address: City Hospital, Cleveland (Dr. Harris); present address: University Hospitals, Cleveland (Dr. Brewster); present address: School of Medicine, Western Reserve University, Cleveland (Dr. Ham).

plete reduction of the blood, increases in such viscosity of from 43% to 115%, respectively, of the values for the same blood samples when oxygenated were observed. It was, therefore, inferred that because the critical oxygen tension for initiation of sickling was close to that of mixed venous blood "a vicious cycle of erythrostasis" might easily be set up in vivo involving increase in viscosity with resultant decrease in rate of blood flow and consequently further deoxygenation of the blood. It thus appeared that the phenomenon of sickling provided a potential mechanism that, if set in motion by a slight increase of plasma viscosity or of rouleaux formation as a result of infection, might understandably produce an extreme degree of erythrostasis. This eventuality seemed to offer an explanation of the hemolytic anemia as well as of the capillary congestion, thrombotic phenomena, and progressive infarction of the spleen characteristic of the disease. Such a concept of the basic pathologic physiology of sickle-cell disease was independently set forth in the same year by Julius Bauer [54] on the basis of clinical and autopsy data and has now received ample confirmation.[25]

Since that time studies by Moore and his associates [1] and by Singer [2] have clearly established that the abnormally increased rate of hemolysis present in sickle-cell anemia is the result of an essential defect of the erythrocyte which allows it only a short span of life. Pauling and his associates [3] demonstrated beyond question that an abnormal molecular species of hemoglobin is present in the erythrocytes of sickle-cell disease. This has led to the recognition and characterization of other genetically determined abnormal varieties of hemoglobin that may occur alone or in combination with sickle hemoglobin. The unique behavior of the abnormal hemoglobin with respect to molecular orientation * appears to account for the bizarre shape changes, birefringence,[18] and increased rigidity of the erythrocyte following deoxygenation that are pathognomonic of sickle-cell disease and its variants.

The present report contains the results of an extension of our earlier studies on the hematology, blood viscosity, and osmotic and mechanical fragilities of the red cells of patients with the sickle-cell anomaly in what are now recognized as its heterozygous and homozygous forms. It includes also further observations of the quantitative effect of sickling upon the mechanical fragility [8] of such red cells originally noted by Diggs and Bibb [30] in 1939. These observations delineate the biologic consequences of the alteration in shape characteristic of the deoxygenated sickle cell: evidence is presented for some of the major steps involved in the mechanism of accelerated erythrocyte destruction and for some of the steps responsible for the circulatory alterations that occur in sickle-cell disease.

METHODS

Conventional hematologic determinations were made from samples of venous blood collected without stasis and rendered incoagulable with a mixture of dry ammonium and potassium oxalate, 200 mg/100 ml. of blood.[5] Hemoglobin determinations were made with the Evelyn photoelectric colorimeter. Erythrocyte counts were made by employing two separate pipettes, from which were filled and counted the two separate chambers of a single hemacytometer; the dilutions were adjusted so that a total of 400 to 600 cells were counted in each chamber. Leucocyte counts were made with a single pipette, and the cells were enumerated in two counting chambers. Hematocrit measurements were made in standard Wintrobe hematocrit tubes after centrifuging at 3000 rpm for 30 minutes in a Size 1 International Centrifuge. Erythrocyte indices were calculated by the method of Wintrobe.[14]

Films of capillary blood from a puncture of the ear lobe were made on coverslips. They were stained with Wright's stain and examined for erythrocyte morphology, and 200 white cells were classified to obtain the leucocyte differential count. Reticulocyte percentages were determined by counting 1000 erythrocytes in similar preparations made with cover slips that had previously been coated with a film of dried 0.4% brilliant cresyl blue in 95% alcohol.

Diagnostic tests for sickling were done with use of 2% sodium metabisulfite † as reducing reagent.[6] The osmotic fragility of red cells was determined on defibrinated venous blood samples, by the quan-

* References 4, 31, and 32.

† Supplied by Eli Lilly & Company.

titative method of Emerson and co-workers,[7] in which the values of tonicity were corrected by formula for the addition of whole blood to the graded solutions of sodium chloride and the effect of pH was corrected to that of pH 7.4. In most instances, in addition to the observations made on an unincubated sample of blood, the erythrocyte osmotic fragility was also determined on blood samples after 24 hours of sterile incubation at 37.5 C with room air as the gas phase. The mechanical fragility of red cells was ascertained for unincubated blood and after 24 hours of sterile incubation, by the method of Shen, Castle, and Fleming.[8] Variations in the techniques as required for special experimental purposes are described below.

All viscosity determinations were made with the Ostwald viscometer on samples of defibrinated blood that had been filtered through several layers of gauze to remove any fibrin particles and then adjusted to a hematocrit value of 35% by the addition or removal of appropriate amounts of the patient's serum. Viscosity readings were made in a constant temperature water bath at 37 C with 4 ml. of the sample in the viscometer. The results are expressed as viscosity relative to distilled water taken as unity. Calculations were made according to the formula of Findlay,[9]

$$\frac{n_1}{n_2} = \frac{t_1 d_1}{t_2 d_2}$$

where

n_1, t_1, and d_1 represent the viscosity, time of outflow in seconds, and density of the sample (determined in a pycnometer of 1 ml. capacity) and

n_2, t_2, and d_2 represent the corresponding values for distilled water.

In order to examine the changes in viscosity of the whole blood at various oxygen saturations of hemoglobin, procedures were devised whereby samples of blood could be equilibrated with various gas mixtures and transferred from equilibrating flasks to the Ostwald viscometer so that the time of flow could be determined without significant exposure to air or to gases other than those originally used.

During the initial phase of this work the object was to relate the changes in per cent sickling, viscosity, and mechanical fragility to the percentage oxygen saturation of hemoglobin. For this purpose random percentage oxygen saturations of the hemoglobin were achieved by deoxygenating the blood samples for various lengths of time in a tonometer containing 100% carbon dioxide. The various measurements (viscosity, per cent sickling, etc.) were then made, and the exact percentage oxygen saturation of hemoglobin was determined by Van Slyke analysis.[10] Data so obtained are plotted against per cent oxygen saturation of hemoglobin in Figures 1, 3, 8, and 9.

In subsequent studies, gas mixtures of known composition were made and stored under pressure in tanks. Blood samples were then equilibrated with these gases in tonometers. The gas mixtures consisted of known percentages of oxygen and nitrogen in the presence of 10% CO_2. The concentration of CO_2 was maintained constant in order to avoid any alterations in pH that would affect cell volume, percentage oxygen saturation, or degree of sickling.[11] The blood samples, 5 to 6 ml. in volume, were equilibrated with the various gas mixtures in glass tonometers. After hydration by bubbling through a sintered glass disc immersed in water, the gas mixture flowed into the tonometer by a needle inserted through a rubber stopper, with a second needle acting as an escape way. The gas mixture streamed over the sample for five minutes, during which time the blood was constantly agitated. At the end of this time, the needles were withdrawn and the tonometer was sealed with collodion and rotated for 20 minutes at 30 rpm and 37 C. This entire procedure was repeated twice more. The blood was then transferred to a viscometer that had previously been flushed through for several minutes with the appropriate gas mixture. If samples were taken for sickling counts, determinations of oxygen content, etc., they were aspirated through the rubber cap of the tonometer into syringes greased and sealed with Hi-Vac lubricant. The various data were plotted against the oxygen tension of the gas sample employed in the equilibration (Figs. 2 and 4).

It was also possible to determine the erythrocyte mechanical fragility of the blood samples at various oxygen tensions. The sample of blood to be tested was introduced into a selected 50 ml. flask which was then closed with a two-hole stopper that had, projecting through one hole, a short glass tube. Attached to the glass tube was a short length of rubber tubing containing the ten 4 mm. glass beads selected for use in the mechanical fragility test. The rubber tubing was partially constricted by a screw clamp below the beads so that they could not enter the flask through the connecting glass tube. Because the internal diameter of the rubber and glass tubes was greater than the diameter of the beads, gas could be blown through the tubing so that equilibration of the blood sample in the flask took place as previously described. After equilibration the second opening of the two-hole stopper was occluded, the rubber tubing was firmly constricted above the glass beads, and the partial constriction below the beads was removed so that they then dropped into the sample of blood to be tested. The procedure thereafter continued during rotation of the stoppered flask containing the beads as with the usual mechanical fragility determinaitons.[8] Appropriate controls

Hematologic Values of Patients

Patient	Sex	Hemoglobin, Gm./100 Ml.	Red Cell Count, Million/Cu. Mm.	Hematocrit Value, %	Mean Corpuscular Volume (MCV), Cu. μ	Mean Corpuscular Hemoglobin Concentration (MCHC), Gm./100 Ml.	Mean Corpuscular Hemoglobin (MCH), μγ	Reticulocytes, %	Icterus Index, Units	White Cell Count, Thousand/Cu. Mm.	Neutrophiles: Adult, %	Neutrophiles: Band, %	Eosinophiles, %	Basophiles, %
Normal values		M, 16±2 F, 14±2	M, 5.4±0.8 F, 4.8±0.6	M, 47±7.0 F, 42±5.0	87±5	34±2	29±2	1±0.5	4-7	5-10	54-62	3-5	1-3	..
A. Sickle-cell trait														
1T	F	13.1	4.62	42.9	93	(31)	28	...	..	8.8	57	(6)	1	..
2T	F	13.2	5.34	41.5	(78)	32	(25)	1.5	3	5.3	(42)	(23)	(5)	1
3T	M	(10.6)	(3.89)	(33.1)	85	32	27	1.3	5	(12.6)	59	(7)	(9)	1
4T	F	(11.8)	(4.12)	38	92	(31)	29	(1.8)	4	(4.0)	55	(25)	3	..
5T	F	13.5	5.30	44.7	84	(30)	(25)	0.8	5	(10.2)	59	(17)	..	1
6T	M	(11.0)	(4.10)	34	83	32	27	0.6	4	8.7	(30)	(10)	15	(2)
7T	F	12.1	5.00	40.2	80	(30)	(24)	0.8	4	...	..	..	..	..
8T†	M	(11.1)	(3.63)	34	94	33	31	1.1	(12)	5.4	47	4	11	2
9T	F	13.0	5.22	40	(77)	32	(25)	...	3	9.4	35	4	3	1
10T	M	15.5	5.57	45.9	82	34	28	(2.5)	..	7.3	(69)	2	1	..
B. Sickle-cell anemia														
1A	F	(8.1)	(2.75)	(23.6)	86	34	27	(7.1)	5	7.4	(43)	(20)	1	..
2A	M	(10.9)	5.05	(35.4)	(70)	(31)	(22)	(9.3)	(10)	9.0	61	(6)	2	1
3A	M	(8.7)	(2.63)	(24.1)	92	33	(33)	(12.8)	(20)	(13.7)	(52)	(1)	(7)	1
4A	F	(7.2)	(3.10)	(22.4)	(72)	32	(23)	(6.6)	(12)	(12.4)	(49)	3	(7)	1
5A	M	(8.1)	(3.15)	(28.2)	90	(29)	(26)	(4.4)	(4)	(10.2)	62	(6)	1	1
6A	F	(8.2)	(2.57)	(25.9)	101	32	(32)	(8.0)	(16)	(12.8)	(43)	5	3	(2)
7A	F	(7.9)	(2.90)	(23.4)	(81)	34	27	(6.0)	(15)	(12.0)	(38)	(10)	1	(2)
8A	F	(6.4)	(2.47)	(21.5)	88	(30)	(26)	(21.0)	(12)	(22.8)	(64)	3	3	1
9A	F	(8.3)	(3.27)	(25.5)	(78)	33	(25)	(13.7)	(10)	(12.8)	(40)	(18)	3	(2)
10A	M	(8.0)	(3.45)	(25.3)	(73)	35	(26)	(3.4)	7	8.5	(51)	(20)	..	..
11A	F	(7.4)	(2.52)	(21.6)	86	34	29	(14.5)	(25)	(17.8)	56	4	(4)	..
12A	F	(5.3)	(1.90)	(17.3)	91	(31)	28	(3.2)	..	(30.0)	(30)	(48)	1	..
13A	M	(7.9)	(2.58)	(23.2)	90	34	30	(6.3)	(12)	8.1	57	3	(4)	(5)

* The values in parentheses are judged to be abnormal. The hematologic data presented here are shown in contrast to the normal as published by Wintrobe.[14] It should be noted, as pointed out by others (References 12 and 15), that the adult Negro populations studied have erythrocyte, leucocyte, hemoglobin, and hematocrit values lower than those presented for the normal Caucasian population.

† Patient 8T had a significant degree of hepatic damage as measured by other liver-function tests.

were prepared and manipulated in the same fashion except that the glass beads were not introduced into the blood.

Before and after some procedures, critical checks were made on the oxygen saturation of the hemoglobin by means of the Van Slyke method. No significant changes were found, indicating that the manipulations required to perform such tests as viscosity or mechanical fragility did not alter the oxygen saturation of the hemoglobin.

Osmotic fragility studies were done on blood samples that had been deoxygenated by equilibration with 90% N_2 and 10% CO_2 in order to produce maximal sickling of the erythrocytes. Without exposure to air the blood samples were then transferred by means of greased tuberculin syringes from the equilibrating flasks into the various stoppered hypotonic solutions of sodium chloride, which had previously been equilibrated with the same gas used for the blood sample. Thus the entire procedure, including the osmotic lysis or survival of the erythrocytes, took place without alteration in the oxygen or carbon dioxide tensions of the environment of the cells.

In all the procedures outlined above, enumeration of the percentage of sickle cells fixed as such by formalin [6] was made as follows: 0.3 ml. of a solution of 10% formalin in 0.85 gm/100 ml. NaCl was placed in a greased tuberculin syringe. Into this was then aspirated 0.1 ml. of the equilibrated blood sample that was to be counted. After the sample was thoroughly mixed by shaking and 5 to 10 minutes were allowed for fixation of the cells, a drop was expelled onto a slide and covered with a cover glass and 1000 erythrocytes were enumerated. It was found unnecessary to equilibrate the formalin-saline solution with the various gas mixtures.

RESULTS AND INTERPRETATIONS

I. Hematologic Data on Patients with Sickle-Cell Trait and Sickle-Cell Anemia

Representative blood cell counts and cell indices of all patients whose blood was em-

with Sickle-Cell Disease *

Meta-myelo-cytes, %	Myelo-cytes, %	Myelo-blasts, %	Lymphocytes			Monocytes		Red Blood Cell Variation						
			Small, %	Large, %	Young, %	Adult, %	Young, %	Size	Shape	Target Cells	Nucleated Red Cells	Nucleated Red Cells/100 WBC	Howell Jolly Bodies, %	Sickled Forms, %
..	..	..	25-33			3-7		....	....	....	....	...	...	...
..	..	..	27	..	..	(9)	..	....	....	....	....	...	...	...
..	..	..	15	1	1	..	..	N	N	0	0	...	...	...
..	..	..	(16)	..	..	7	(2)	N	N	0	0	...	...	...
(2)	..	..	(8)	..	(1)	(2)	(4)	N	N	0	0	...	...	...
..	..	..	(13)	..	..	(10)	..	N	N	0	0	...	...	...
..	..	..	(35)	4	..	4	..	N	N	0	0	...	...	...
..	..	..	..	..	..	..	..	N	N	0	0	...	...	...
..	..	..	23	2	..	6	..	+ (Mac)	N	0	0	...	...	...
..	..	..	51	1	..	5	..	N	N	0	0	...	...	...
..	..	..	(18)	..	..	(1)	(1)	N	N	0	0	...	...	...
..	..	..	23	2	..	(11)	..	+++	++	++	+	3	0	0.3
..	..	..	(12)	(1)	(1)	(16)	..	+++	++	++	....	1	0	2.6
..	..	..	26	..	..	(11)	..	++	++++	++	....	1.5	0.2	24.3
..	(1)	..	25	2	(1)	5	..	++	+	+	....	0	0.4	3.0
..	..	..	(17)	..	..	(9)	..	++	+	++	....	0	...	0.2
(2)	..	..	23	2	(1)	4	(5)	++	+	+	....	1.0	...	0.8
(4)	(1)	..	(34)	..	(1)	(10)	..	+++	+++	++	+	5.0	0.6	16.0
..	..	..	(20)	..	..	(9)	..	+++	++	++	....	4.5	0.1	10.0
..	..	..	(22)	..	..	(11)	(3)	++ (Mac)	++	+	....	...	...	0.8
(3)	..	..	(12)	(6)	..	(11)	..	++	+	+++	....	...	...	1.4
(4)	..	..	31	..	(1)	(1)	..	+++	++++	++	....	2	0.2	11.9
..	..	(3)	(6)	..	..	(8)	..	++	N	0	++	+	0.2	0.6
..	..	..	(16)	(4)	(1)	(8)	(2)	....	....	....	....	...	...	...

ployed for the various studies reported here are shown in the Table. Only patients who showed the typical clinical and laboratory findings consistent with the diagnoses of sickle-cell anemia (homozygous state) and sickle-cell trait (heterozygous state) [12] are included. Although this work was completed before methods of paper electrophoresis of hemoglobin were available, our recent studies have shown that cells from patients known to have sickle-cell-hemoglobin-C disease and those from patients with sickle-cell-thalassemia disease behave quite differently with respect to erythrocyte mechanical fragility, sickling, and whole blood viscosity changes at the various oxygen tensions.[13] These facts together with the relative paucity of target cells found on peripheral blood smears justify the assumption that the patients studied here were true single homozygotes or heterozygotes with respect to the sickling gene and did not have other hereditary defects of hemoglobin or red cells, i. e., had true sickle-cell anemia or sickle-cell trait.

The patients with sickle-cell anemia all showed a significant degree of anemia, the erythrocytes being normocytic and normochromic in about one-half of the patients and microcytic, slightly hypochromic in the rest. In none of the patients with hypochromic microcytic type of cells were the indices significantly altered following adequate, prolonged oral administration of iron. The characteristic increases in reticulocytes, leucocytes, and icterus index were present. The variation in size and shape of the erythrocytes as observed in stained films of blood showed considerable abnormality when graded on an arbitrary scale, from 1+ to 4+.

The hematologic picture of the patients with sickle-cell trait showed only minor deviations from the normal, in contrast to that presented by the patients with sickle-cell

anemia. Thus, the reticulocyte counts, erythrocyte characteristics, and icterus indices were essentially normal. Patient 8T was known to have hepatic involvement associated with chronic alcoholism, in addition to sickle-cell trait.

II. Effect of Deoxygenation on the Percentage of Sickle Cells in Sickle-Cell Anemia and Sickle-Cell Trait

Since the vast majority of the erythrocytes in patients both with sickle-cell anemia and with sickle-cell trait can assume the sickled form, what differences explain the presence of clinical signs and symptoms and continuing cell destruction in the anemia (homozygous disease) and the almost complete absence of these findings in patients with sickle-cell trait (heterozygous disease)?

The percentages of sickled erythrocytes throughout the complete range of oxygen saturations are shown in Figure 1. As the oxygen is removed from the intracellular hemoglobin the erythrocytes assume the sickled form in increasing numbers, according to the sigmoid-shaped curves shown in Figures 1 and 2. There is clear separation in behavior between the cells from patients with anemia and those from patients with the trait. As shown in Figure 1, the cells in anemia‡ begin to show sickling shape changes with the oxygen saturations of the hemoglobin in the range of 60% to 90%; at 40% saturation 75% or more of the cells are in sickled form. In contrast to this, cells in the trait begin to sickle only at 30% to 50% oxygen saturation; not until 20% oxygen saturation are 75% of the cells sickled. It is only in the very low ranges of oxygen saturation that the majority of cells from both types of blood are in the sickled form. It is also apparent from Figures 1 and 2, and from the morphology of the red cells in blood films made in air given in the Table, that some of the cells from patients with anemia remain in the sickled form even at 100% oxygen saturation. Cells of this type were not seen in the blood of patients with trait. These so-called permanently sickled or irreversibly sickled cells [16] lack the delicate filamentous extremities displayed by cells sickled in vitro. By analogy with in vitro incubation studies there is evidence [16] to support the hypothesis that this permanent shape change may be brought about by in vivo stagnation and sequestration. If so, these processes do not occur to a significant degree in patients with the sickle-cell trait.

In Figure 2 the percentages of sickled cells are plotted against the oxygen tension of the blood sample expressed in millimeters of mercury; the blood samples were equilibrated with a gas mixture containing a constant 10% concentration of CO_2 with different concentrations of O_2 and N_2. The results and their interpretations are the same as mentioned above for Figure 1 and differentiate clearly the behavior of the cells from patients with anemia and with trait. It should be appreciated, however, that the data obtained by the two different methods of gas equilibration used in Figures 1 and 2, respectively, are not entirely comparable. Thus, when 100% CO_2 was used to obtain the various degrees of hemoglobin unsaturation, the oxygen tension of the blood sample was lowered inversely to the CO_2 tension. Also, the pH of each sample varied according to its final CO_2 tension, whereas the pH value of samples equilibrated with gas mixtures uniformly containing 10% CO_2 was constant.

Interpretation.—It has long been known that for sickling to take place the hemoglobin must be changed from the oxygen-saturated to the oxygen-unsaturated form.[17] Scriver and Waugh [20] and then Sherman [18] demonstrated that the number of cells in the sickled form is inversely proportional to the oxygen tension of the blood sample and that sickling begins at a much higher oxygen tension in the anemia than in the trait. In this work the oxygen tensions were regulated by various degrees of partial vacuum, with no con-

‡ For brevity in this manuscript the term "anemia" will be used to indicate the homozygous sickle-cell anemia; "trait" will be used to indicate the heterozygous sickle-cell trait.

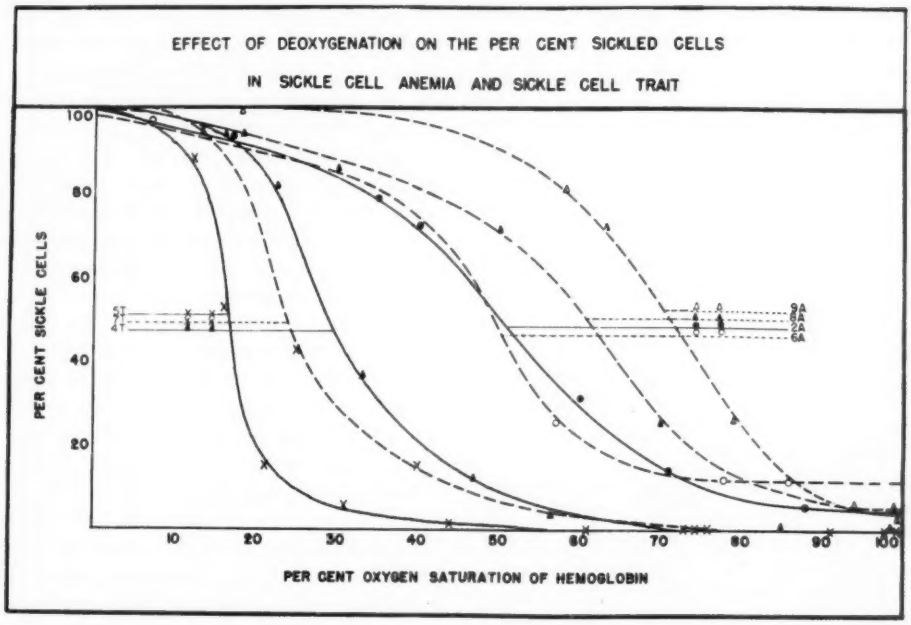


Fig. 1.—Case numbers in this and subsequent figures correspond with those of the Table. For complete deoxygenation, 100% CO_2 was used.

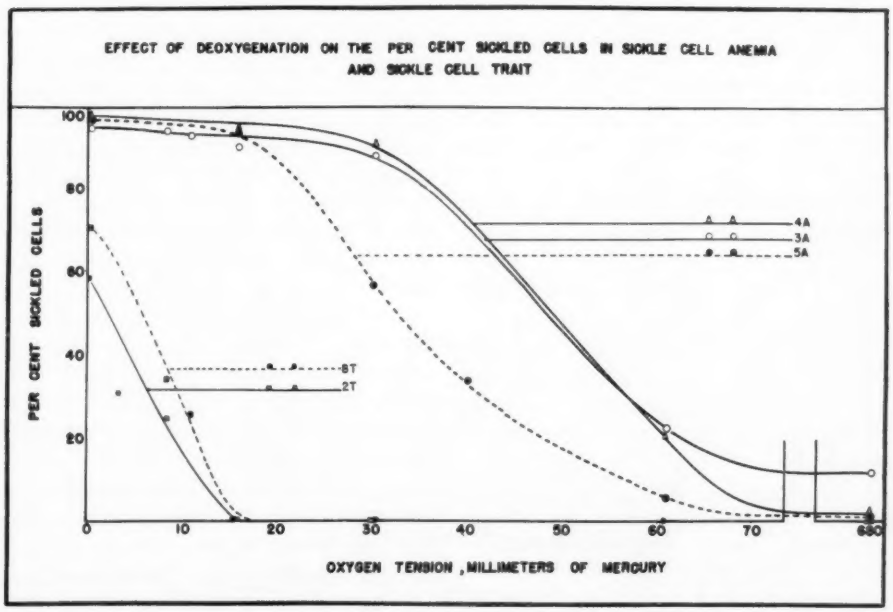


Fig. 2.—The CO_2 concentration was maintained constant at 10% for all gas mixtures.

trol of the hydrogen ion concentration. Hahn and Gillespie [19] had shown that to an optimal point an increase in hydrogen ion concentration increased the degree of sickling and that the cells of anemia were more susceptible to these changes than were the trait erythrocytes. However, it was not until Lange and co-workers [11] published their results on the effects of oxygen tension and pH on the sickling phenomenon, done with measurement and adequate control of the various factors involved, that the quantitative relations were established. This work showed conclusively that erythrocyte sickling is related inversely to the oxygen tension and that trait erythrocytes are more resistant to changes in both pH and oxygen tension than are the anemia cells. The studies reported here confirm these findings (Figs. 1 and 2). (No studies were made to ascertain the effect of various hydrogen ion concentrations in the present measurements.) In addition, the actual state of oxygen saturation of the hemoglobin was directly measured, since, for any given condition, this determines the shape change of the erythrocyte. The data obtained for the six patients examined by this oxygen saturation method agree closely with those obtained on five patients by oxygen tension studies made at constant pH, which are perhaps more readily interpretable in the light of clinical findings. The oxygen tension in tissue probably varies between the limits of 15 and 42 mm. Hg.[20] Even when allowance is made for the slight increase in sickling in the anemia cell due to the 10% CO_2 used, it is readily appreciated by reference to Figure 2 that sickling takes place in the range of physiologic oxygen tensions in erythrocytes of patients with the anemia. Conversely, sickling occurs only in the oxygen tensions produced by artificial laboratory conditions in the erythrocytes of the trait.

III. Effect of Deoxygenation on the Viscosity of Whole Blood in Sickle-Cell Anemia and Sickle-Cell Trait

The effects of deoxygenation upon the viscosity of samples of sickle-cell blood are shown in Figures 3 and 4. The viscosity readings are plotted against the percentage oxygen saturation of the hemoglobin in Figure 3 and against the oxygen tension in millimeters of mercury in Figure 4. Since the absolute maximal increase in viscosity of the blood varied from patient to patient, these changes in viscosity are plotted as per cent of the maximal increase (at complete deoxygenation) in order conveniently to compare the behavior of one blood sample with another. Although some of the variations in absolute viscosity may have been the result of small errors in the adjustment of oxygenated hematocrit values exaggerated in the deoxygenated state, no completely adequate explanation for the differences in absolute viscosity values is apparent, as is discussed below in this section. All blood samples were adjusted to a hematocrit value of 35%, because of the marked effect of hematocrit values on the viscosity of normal blood.[21] However, it was realized that if the erythrocytes were somewhat hypochromic or microcytic such samples of blood, after adjustment of the hematocrit level, would contain either more hemoglobin or more erythrocytes, respectively, per cubic millimeter than would a sample with normocytic, normochromic erythrocytes. Although the number and size of particles suspended in a fluid medium is known to influence the viscosity of the suspension,[22] no significant correlation was found here between these factors and the increases in absolute viscosity. Therefore, unknown factors that presumably affect the degree of distortion or rigidity of the sickled form seem to have exerted significant influences on the red cell. However, it is apparent that the percentage oxygen saturation of the hemoglobin, by giving the ratio of oxygenated to unoxygenated hemoglobin, also gives a direct measure of the actual state of the intracellular hemoglobin molecules with respect to the basic mechanism of sickling. This relation can also be ascertained indirectly from the oxygen dissociation curve of the blood sample, its pH, and its oxygen tension. It is apparent from the curves in Figures 3 and 4

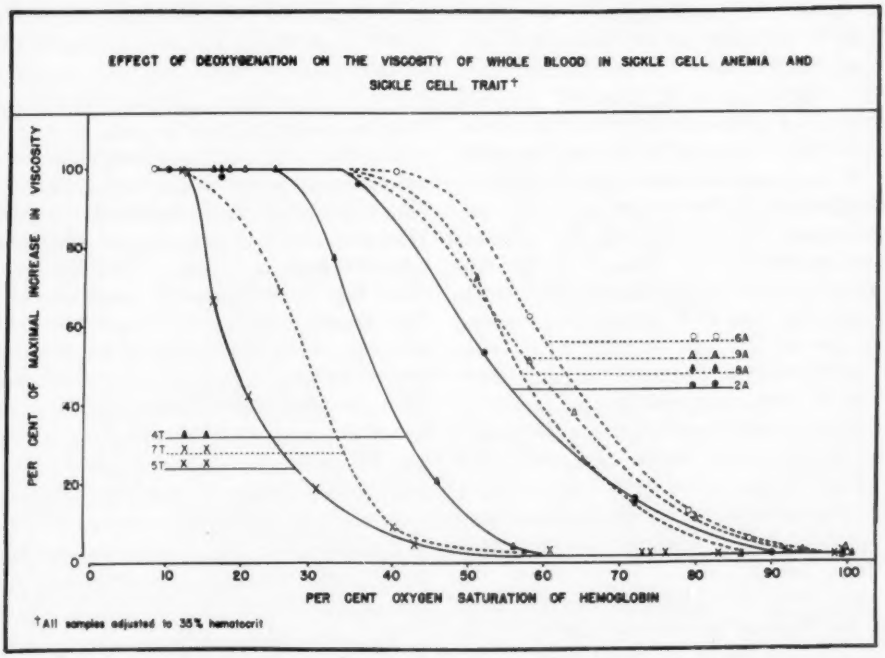


Fig. 3.—For complete deoxygenation, 100% CO_2 was used, as shown in Figure 1.

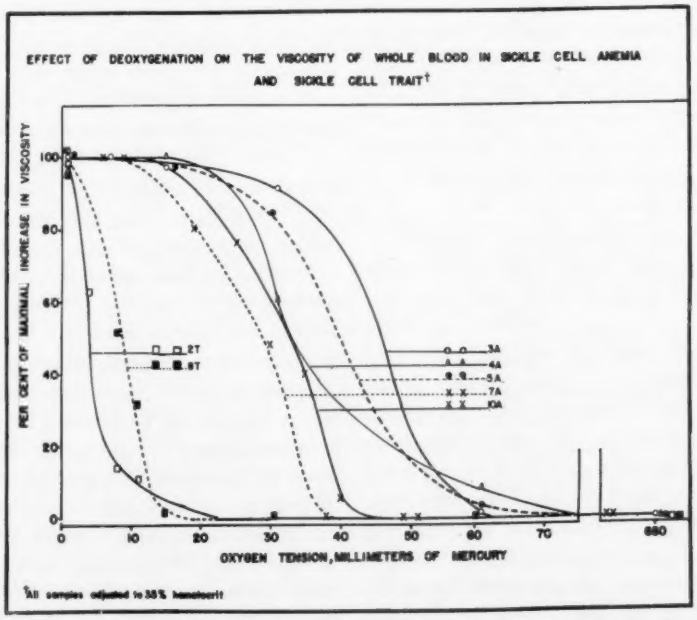


Fig. 4.—The CO_2 concentration was maintained constant at 10% for all gas mixtures, as shown in Figure 2.

that as the oxygen saturation of the hemoglobin is decreased an increase in the viscosity of the whole blood sample takes place, according to a sigmoidal type of curve, until a maximum is reached. Also, the degree of increase in viscosity appeared to be of a magnitude that would be of clinical significance. Thus, whereas 4 to 5 minutes might be required for the oxygen-saturated blood to flow through the Ostwald viscometer the oxygen-unsaturated sample would take from 15 to 20 minutes or more. The internal diameter of the capillary bore of the Ostwald viscometer is certainly enormous in comparison with that of capillaries or of postcapillary venules, where the oxygen tension would be lowest. Therefore, any slowing of flow through the Ostwald capillary tube due to sickling would presumably be greatly magnified in vivo in such small vessels.[22]

The change in viscosity is directly related to the increase in the number and very probably the degree of sickled forms in the sample. With the assumption of the rigid and bizarre shapes of the erythrocytes, the internal friction of the suspension is increased and flow is impeded. All these changes were completely reversible with oxygenation for blood from cases of both the anemia and the trait. No detectable viscosity changes occurred in samples of normal blood that were subjected to the same variations in oxygen saturation.

It is apparent that the blood from patients with the anemia behaves very differently from that of patients with the trait. The increases in viscosity in the anemia begin in the higher ranges of oxygen saturations. At 40% saturation all samples had shown 85% or more of their maximal increase in viscosity, whereas in only one sample from the trait had as much as 35% of the maximal change taken place. In the four other trait samples less than 10% increase had occurred.

Interpretation.—Thus the shape changes of the erythrocytes are not only responsible for effects on the red cell itself but also profoundly alter the characteristics of the whole blood. In 1940 Ham and Castle reported whole blood viscosity studies made on two patients with sickle-cell anemia.[23] Results of a technique differing only slightly from that described here, the data have been recalculated and incorporated into the material here presented as cases 7A and 10A. The viscosity increases indicated by these measurements were marked and allow the inference that an enormous impedence to blood flow would occur in small vessels.[22] The viscosity changes follow directly the changes in the characteristics of the red cells and the increase in numbers of sickled forms. Thus the plastic cell becomes rigid and distorted in shape while acquiring the typical long filamentous end-processes; the distorted cells become entangled and enmeshed one with another so that the internal friction of the suspension rises, apparently resulting in an increased viscosity and slowing of the rate of flow.

Just as the marked differences in the positions of the viscosity curves of anemia and trait presumably depend on the differences in concentrations of sickle-cell hemoglobin, it is probable that the smaller differences in the positions of the viscosity curves of the bloods of patients either with anemia or with trait are dependent in part on the proportion of sickle-cell hemoglobin present in any given patient. Those with the higher proportion of sickle-cell hemoglobin probably show beginning changes at slightly higher oxygen saturations than the others. However, no electrophoretic analyses were done to determine the percentages of abnormal hemoglobin present. Also, the role of other factors that may influence the degree of sickling of the cells are impossible to assess or apply to the present findings. For example, Singer[24] reports that the fetal hemoglobin may not be equally distributed in all cells and Lange and co-workers[11] noted that hypertonic sodium chloride increases the susceptibility of the cells to the sickling effect of low oxygen tensions. In the present studies no correlations could be made between the mean corpuscular hemoglobin

concentration (MCHC) of the cells and the position of the viscosity curve, although under unusual and extreme circumstances this has been shown.[35]

For the patients with the anemia the increases in sickling and in viscosity begin in the physiologic range of oxygen tensions, but for the trait these occur only in the artificially low ranges, usually considered nonphysiologic. The possible consequences of these differences would appear to be manifold. The most evident is that of the production of a vicious cycle in the anemia in which the following events may be assumed to take place within the physiologic range of oxygen tensions: In the capillaries of various organs—particularly those with slow blood flow—oxygen may be given up by the blood to such a degree to meet the metabolic demands of adjacent tissue that the red cell becomes altered to the sickled form. Concomitant with a rise in the number of the sickled forms the viscosity of the blood increases so that circulation may be impeded first in the distal ends of the capillaries, with the result that more and more oxygen is removed from the red cells traversing the capillaries by continuing tissue requirements. Moreover, as stasis is prolonged, the hydrogen ion concentration of the tissue and blood may increase, with resultant further unloading of oxygen and further facilitation of the sickling process. This may eventually result in the formation of a static mass of sickled cells in capillaries and venules. This concept of the disturbance in circulatory physiology implies that the oxygen tension at which the first change in viscosity occurs may be the most important factor, since it may serve as the trigger mechanism for the initiation of the vicious cycle. Thus it is proposed that the physical consequences of the vicious cycle so defined explain in large part the striking vascular manifestations of sickle-cell anemia [25] and the changes in the red cells leading to their increased rate of destruction.

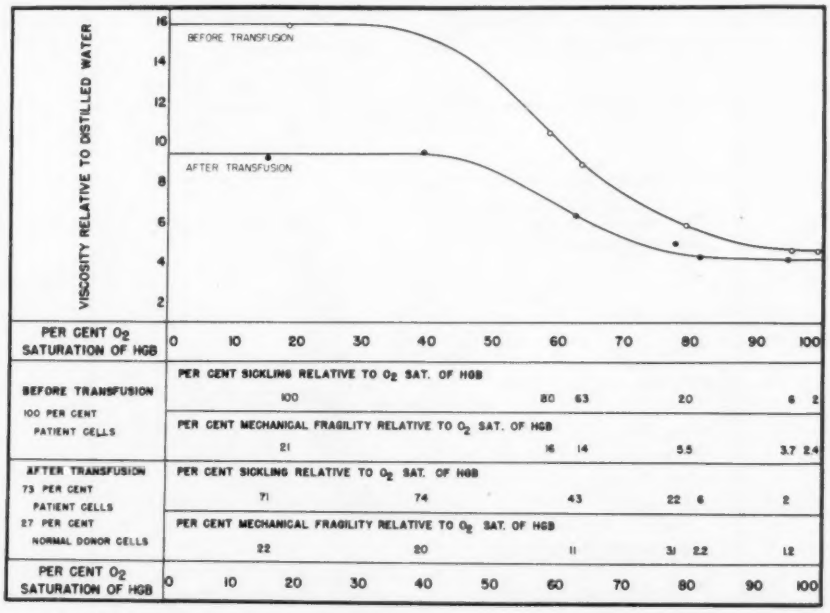

VISCOSITY RELATIVE TO DISTILLED WATER
16
14
12
10
8
6
4
2
BEFORE TRANSFUSION
AFTER TRANSFUSION
PER CENT O_2 SATURATION OF HGB
0 10 20 30 40 50 60 70 80 90 100
BEFORE TRANSFUSION
100 PER CENT PATIENT CELLS
PER CENT SICKLING RELATIVE TO O_2 SAT. OF HGB
100 80 63 20 6 2
PER CENT MECHANICAL FRAGILITY RELATIVE TO O_2 SAT. OF HGB
21 16 14 5.5 3.7 2.4
AFTER TRANSFUSION
73 PER CENT PATIENT CELLS
27 PER CENT NORMAL DONOR CELLS
PER CENT SICKLING RELATIVE TO O_2 SAT. OF HGB
71 74 43 22 6 2
PER CENT MECHANICAL FRAGILITY RELATIVE TO O_2 SAT. OF HGB
22 20 11 3.1 2.2 1.2
PER CENT O_2 SATURATION OF HGB
0 10 20 30 40 50 60 70 80 90 100

Fig. 5 (Case 9A).—Preoperative transfusion study. In relation to the per cent oxygen saturation, the Figure illustrates the changes in viscosity, per cent sickled cells, and mechanical fragility brought about by transfusing normal cells into the patient so that the final cell population was approximately 70% patient cells and 30% normal donor cells.

In a patient with sickle-cell anemia, Case 7A, pneumonectomy was required for pulmonary tuberculosis. It was feared that a sickle-cell crisis might be precipitated by a possible period of anoxia during the operative procedure. Accordingly, the patient was transfused with compatible normal cells which would not participate in the increased sickling, mechanical fragility, and blood viscosity that have been mentioned. To test the quantitative effect of anoxia on these characteristics of the blood, studies were done before as well as after transfusion, when approximately 30% of normal donor cells were circulating in the peripheral blood. The results are compared in Figure 5. The number of cells that could be made to sickle by complete anoxia corresponded closely with the number of patient-cells known to be present by differential Ashby count. Comparing the number of sickle cells present before and after transfusion, namely, 100% and 70%, there was a decrease in viscosity roughly proportional to the number of normal cells present. The unaltered mechanical fragility remains unexplained. The patient received further transfusion during the operation, which was uneventful, as was the postoperative period.

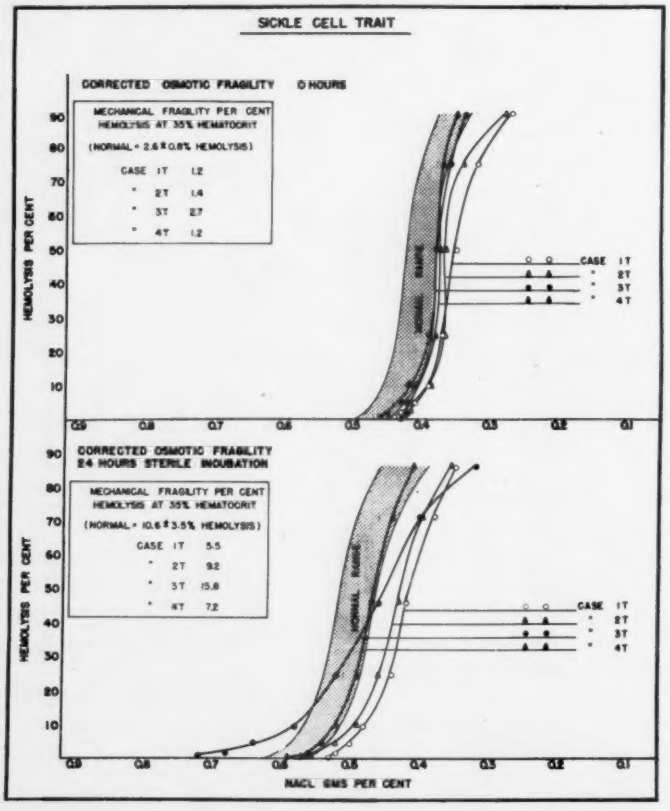


Fig. 6.—Erythrocyte osmotic and mechanical fragility in patients with sickle-cell trait. The top portion of the chart shows results before incubation; the lower portion shows results after 24 hours sterile incubation of the blood sample. Results have been corrected according to the formula of Emerson and co-workers [7] and have been compared with the normal ranges as determined by them, as shown in the shaded areas, which indicate the mean ±.

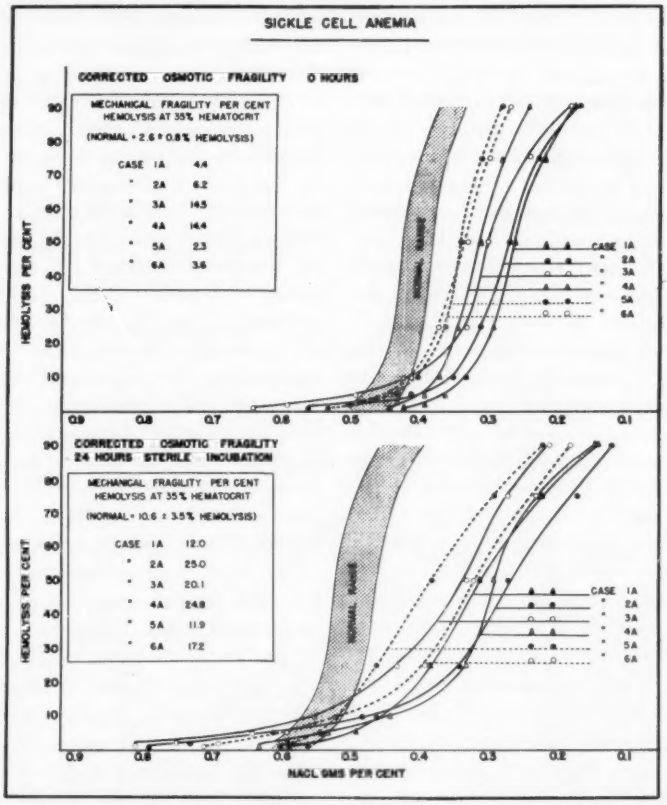


Fig. 7.—Erythrocyte osmotic and mechanical fragility in patients with sickle-cell anemia. The top portion of the chart shows results before incubation; the lower portion shows results after 24 hours sterile incubation of the blood sample. Results have been corrected and plotted as in Figure 6.

IV. Osmotic and Mechanical Fragilities of Erythrocytes from Patients with Sickle-Cell Anemia and Sickle-Cell Trait

Curves illustrating the "osmotic fragility" of erythrocytes of patients with sickle-cell trait and anemia are shown in Figures 6 and 7. Osmotic fragility is regarded as a measure largely of the difference between the volume of red cell and that of a sphere of equal surface: increased osmotic fragility thus indicates increased spheroidicity.[27] It is apparent that there are differences in the characteristics of the erythrocytes in the anemia when compared to those of both the trait and the normal. The osmotic fragility of the anemia cells is shown by a family of curves in Figure 7, the main body of which falls to the right of and well outside the normal range in the direction of increased resistance to osmotic lysis. By analogy with findings in iron deficiency this is consistent with the slightly hypochromic and therefore inferentially "flat" nature of some of the erythrocytes. However, some other cell "flattening" factor must also be operative, since some of the samples tested were not significantly hypochromic or microcytic (Table, Cases 1A, 3A, and 6A). Indeed, some of the hypochromic microcytic cells were less resistant osmotically than those with normal indices. There is, in addition, another osmotic abnormality. Uniform populations of other types of cells with a

low mean corpuscular hemoglobin concentration do not show a portion with increased susceptibility to osmotic hemolysis as do here the erythrocytes in the sickle-cell anemia. Thus, the "trails" to the left of the normal range indicating an increased osmotic susceptibility of a portion of the red cells shown in four of the curves from anemia patients are significantly abnormal. After sterile incubation of the anemia blood for 24 hours both types of osmotic alteration became exaggerated, as shown in Figure 7. In contrast to these findings, the osmotic fragility of cells from the trait, as shown in Figure 6, are represented by a family of fairly uniform curves, which are approximately at the lower limits of the normal range or show a slightly increased osmotic resistance. None showed the "trail" indicative of cells with increased susceptibility to osmotic lysis. Except for Case 3T, which resembled the results in anemia, the changes induced by 24-hour incubation of trait cells were scarcely abnormal. Thus, the erythrocytes of the anemia had abnormal osmotic fragility characteristics in both the unincubated and incubated samples, while those of the trait differed only slightly from the normal.

The mechanical fragility of the red cells of both anemia and trait (Figs. 6 and 7) was studied after equilibration of the samples with room air, and the results were compared with the normal range reported by Emerson and co-workers.[7] The mechanical fragilities of the erythrocytes from patients with the anemia were significantly increased above normal in four of six patients (Cases 1A, 2A, 3A, and 4A) when measured before incubation and in four patients (Cases 2A, 3A, 4A, and 6A) when measured after 24 hours of sterile incubation. In four patients with the trait the erythrocytes had a normal mechanical fragility when unincubated and normal values after incubation except for Case 3T, which likewise showed abnormalities in osmotic fragility.

By means of the special procedure described under Methods, the osmotic behavior of the erythrocytes of two of the patients with the anemia was examined when the cells were oxygenated (discoidal form) and also when they were deoxygenated (sickled form). These curves are not corrected for pH and tonicity alterations, since the blood samples as well as the tubes of saline were all equilibrated with gases containing 10% CO_2 and the results may be compared one with the other and with the normal values. As illustrated in Figure 8, there is no apparent difference in the osmotic behavior of the erythrocytes, whether oxygenated or deoxygenated. Similar osmotic fragility determinations were also performed after 24 hours of sterile incubation, during which time the cells had been maintained in oxygenated or deoxygenated forms. After sterile incubation for 24 hours in the oxygenated state (Portions A and B) no significant differences in the osmotic tests were observed when these were subsequently done with the cells in either the oxygenated or deoxygenated state. However, after sterile incubation for 24 hours in the deoxygenated form (Portions C and D) significant differences in osmotic fragility were observed. Thus, when the test was subsequently done with the cells in the deoxygenated state the curve of osmotic fragility indicated a markedly increased resistance to osmotic lysis. The oxygenated cells showed a curve indicating less increase in resistance than did the corresponding deoxygenated sample. By similar techniques measurements have been obtained with both unincubated and incubated samples of blood from normal subjects and from patients with Cooley's anemia. In these conditions there was no difference between oxygenated and deoxygenated samples.

Interpretation of Osmotic Fragilities.—The conventional osmotic fragility test can be used to demonstrate certain morphological abnormalities of red cells. Water is moved across the cell membrane by the osmotically active intracellular components to effect dissolution of the restraining forces of the membrane. A shift of the osmotic fragility curve indicating increased resistance indicates that

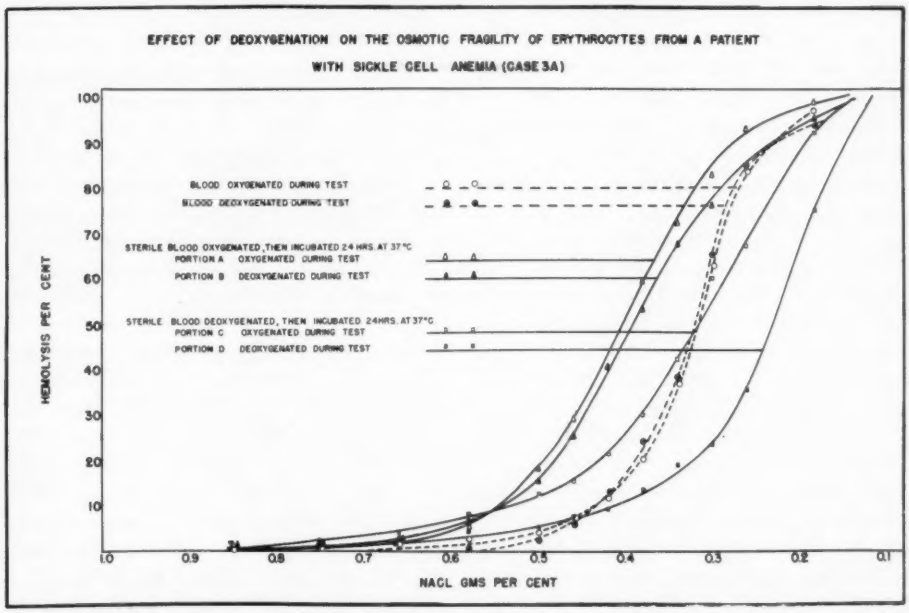

EFFECT OF DEOXYGENATION ON THE OSMOTIC FRAGILITY OF ERYTHROCYTES FROM A PATIENT
WITH SICKLE CELL ANEMIA (CASE 3A)
HEMOLYSIS PER CENT
NACL GMS PER CENT
BLOOD OXYGENATED DURING TEST
BLOOD DEOXYGENATED DURING TEST
STERILE BLOOD OXYGENATED, THEN INCUBATED 24 HRS. AT 37°C
PORTION A OXYGENATED DURING TEST
PORTION B DEOXYGENATED DURING TEST
STERILE BLOOD DEOXYGENATED, THEN INCUBATED 24HRS. AT 37°C
PORTION C OXYGENATED DURING TEST
PORTION D DEOXYGENATED DURING TEST

Fig. 8.—There was no difference in osmotic fragility between oxygenated and deoxygenated samples of unincubated blood. For blood incubated for 24 hours in the oxygenated state, there was an increase and similar osmotic fragility when tested (Portions A and B). However, for blood incubated for 24 hours in the deoxygenated state (sickled form) there was marked increased resistance for the sample tested in the deoxygenated state and less resistance (Portion C) for the sample oxygenated for test.

more water can enter the cell before lysis takes place at the critical spherical form.[27] In addition, the incubation technique of Ham and Castle [26] can reveal cellular defects that may remain latent with the ordinary test. The exact mechanisms producing the changes that follow incubation are not known but probably involve changes in membrane strength and permeability as a result of disturbances in cell energy sources.[56] From the inspection of the four sets of curves in Figures 6 and 7, it seems apparent that, so far as osmotic behavior is concerned, the cells in the anemia are distinctly abnormal while those in the trait are only slightly tainted. As mentioned previously, increased osmotic resistance as seen here is usually indicative of a "flat" erythrocyte that is poorly filled with hemoglobin, such as are observed in Cooley's anemia, hypochromic anemia, or in the acquired erythrocyte changes associated with infectious hepatitis or jaundice.[23] Hemoglobin itself, compared with cell electrolytes, has little osmotic influence but may, as in hereditary spherocytosis, seem to "inflate" the cell towards its spheroidal form. However, the cells in sickle-cell anemia are increased in resistance but, according to the available measurements, they are neither flat nor poorly filled with hemoglobin. Another possible explanation is alteration of the cell membrane so that it may either stretch beyond the normally critical spherical shape or withstand osmotic pressure stresses to an abnormal degree. More probable, however, is an abnormality of the membrane (or of some other cell characteristic) permitting loss of osmotically active substances. Red cells in the sickled form readily lose potassium,[33] and "permanently" sickled red cells are characteristic of the peripheral blood of patients with sickle-cell anemia but not of those with sickle-cell trait.[16] Susceptibility to loss of osmotically active substances other than hemoglobin could be consistent with

Sharpsteen's § findings of a decrease by 1 to 3 atmospheres in the osmotic pressure of sickle cells and with the abnormal increase in osmotic resistance upon incubation.

The cellular changes that take place during sterile incubation at 37 C have been discussed by Emerson and co-workers.[7] It appears that the erythrocytes from patients with the anemia present numerous metabolic abnormalities.[18] At present, it is impossible to predict the resultant effect on the osmotic behavior of such abnormalities as the reduction in the rate of turnover of total phosphorous,[58] the abnormal sodium and potassium content,[33] and the abnormal loss of potassium and gain of sodium upon deoxygenation.[34] Actually, the erythrocytes from patients with sickle-cell anemia present a double problem in this regard, for, although the major portion of the erythrocytes shows increased resistance to osmotic stress and becomes even more resistant after incubation, a certain proportion of the cells shows increased fragility and, again, this fragility is further increased by incubation. In the latter aspect these results resemble the incubation studies of Ham and Castle and are interpretable in the light of the work of Selwyn and Dacie. Those cells showing increased osmotic fragility on both the direct and incubated tests are more nearly spherical than normal. Increase in spheroidicity of normal erythrocytes is produced in vitro by incubation procedures, and it is postulated that the sickle anemia cells showing increased osmotic fragility are the ones which have been selectively sequestrated and, in effect, incubated in vivo.[16] Further laboratory incubation serves to accentuate these changes. The process whereby the cells become sequestered in vivo will be presently discussed. After incubation, the changes in osmotic behavior of erythrocytes from patients with sickle-cell trait are, again, somewhat intermediate between those of normal subjects and those with sickle-cell anemia.

Osmotic fragility tests were also performed on oxygenated and deoxygenated samples of unincubated sickle-cell blood by means of special techniques in an attempt to determine the osmotic behavior of the erythrocytes while in the sickled state. As can be seen in Figure 8, the osmotic fragilities of the unincubated samples were essentially the same whether the cells were oxygenated or deoxygenated. On first consideration, it would appear most likely that a cell distorted into the sickle form would change its osmotic characteristics. It is emphasized that the experimental conditions were such that the hemoglobin remained in the reduced form all during the test. Indeed, when counts were made of the sedimented intact cells in the tubes of hypotonic saline solution containing the deoxygenated blood samples, values of over 95% sickling were consistently found in the concentrations down to 0.58 gm. NaCl/100 ml. In more hypotonic concentrations the percentage of sickled cells decreased in approximate proportion to the amount of lysis taking place. From work by Guest [29] on the sickle cell it has been shown that in hypotonic solutions of sodium chloride the cell increases to a maximal swelling of 175% of its initial volume before rupture. It would seem probable then that in the lower saline tonicities the cell absorbs water to the extent that the sickle hemoglobin is diluted below the concentration at which a tactoid can be maintained. Thus, after enough water enters, even with the hemoglobin in the reduced form, the cell is no longer distorted into the sickled shape and its osmotic behavior becomes essentially the same as that of the oxygenated cell. Presumably, the same mechanism obtains in the results with the samples incubated for 24 hours. However, it has been demonstrated [16] that only a small proportion of the cells will sickle after blood has been incubated in the oxygenated state for 24 hours. Conversely, after incubation in the deoxygenated state for 24 hours a certain number of the cells become

§ Reference 28 and Sharpsteen, J. R., Jr.: Osmotic Behavior of Red Cells in Hemolytic Phenomena, read before the National Meeting of the American Federation for Clinical Research, Atlantic City, N. J., May 4, 1952.

irreversibly sickled and do not resume the discoid form on reoxygenation.[16] The increased resistance to osmotic lysis of the sample incubated in the deoxygenated state might be explained on the basis of increased potassium or other electrolyte loss or as due to membrane stretching resulting from prolonged sickling.[34] The difference between the osmotic fragilities of the subsequently oxygenated and deoxygenated Portions C and D, although inexplicable at present, may merely express a further loss of potassium by Sample D. It was consistent and reproducible and was not seen in normal subjects or in patients with Cooley's anemia.

Mechanical Fragility.—In Figure 9 are shown the results of mechanical fragility tests of anemia and trait blood of various oxygen saturations. These findings are in keeping with those of Lange and coworkers.[11] The mechanical fragility of the erythrocytes increases markedly as the hemoglobin is deoxygenated and the cells assume the sickled form. As would be expected from the results of the preceding experiments, the procedure again contrasts the behavior of the cells in the anemia and in the trait. No increase of mechanical fragility of the trait cells occurred until an oxygen saturation of hemoglobin had been reached at which the mechanical fragility of the anemia cells had reached nearly their maximal increase under the conditions of the test. Normal erythrocytes show no change in mechanical fragility when tested under these circumstances.

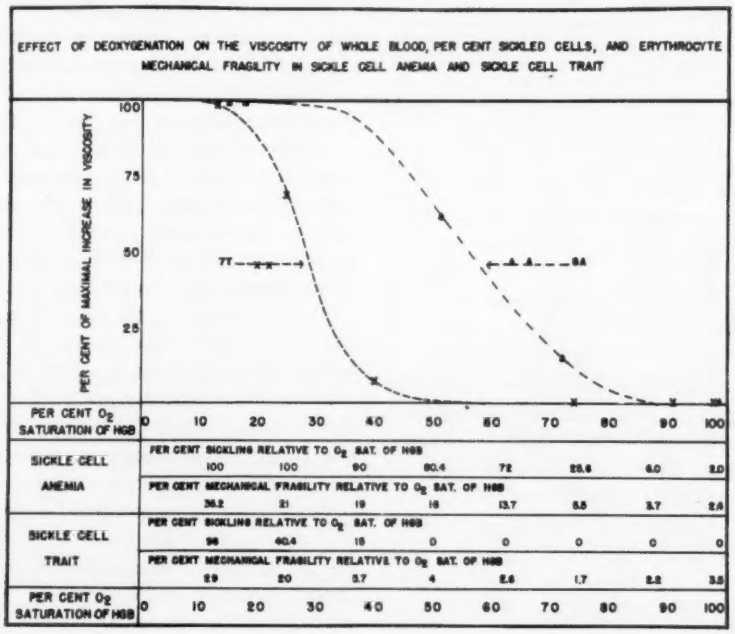

EFFECT OF DEOXYGENATION ON THE VISCOSITY OF WHOLE BLOOD, PER CENT SICKLED CELLS, AND ERYTHROCYTE MECHANICAL FRAGILITY IN SICKLE CELL ANEMIA AND SICKLE CELL TRAIT
PER CENT OF MAXIMAL INCREASE IN VISCOSITY
100
75
50
25
77
64
PER CENT O2 SATURATION OF HGB
0 10 20 30 40 50 60 70 80 90 100
SICKLE CELL ANEMIA
PER CENT SICKLING RELATIVE TO O2 SAT. OF HGB
100 100 90 80.4 72 28.6 6.0 2.0
PER CENT MECHANICAL FRAGILITY RELATIVE TO O2 SAT. OF HGB
36.2 21 19 16 13.7 5.5 3.7 2.6
SICKLE CELL TRAIT
PER CENT SICKLING RELATIVE TO O2 SAT. OF HGB
96 40.4 18 0 0 0 0 0
PER CENT MECHANICAL FRAGILITY RELATIVE TO O2 SAT. OF HGB
29 20 3.7 4 2.6 1.7 2.2 3.5
PER CENT O2 SATURATION OF HGB
0 10 20 30 40 50 60 70 80 90 100

Figure 9

Interpretation of Mechanical Fragilities.—The mechanical fragility test [8] was employed as an arbitrary in vitro procedure to quantitate certain red cell abnormalities. The mechanical fragility so measured may or may not be related to the in vivo life span of the erythrocytes, in some instances. In sickle-cell disease, if increase in mechanical fragility is an essential part of the mechanism of destruction of the erythrocyte then, theo-

retically, the cells should be most susceptible to mechanical trauma when in the sickled form. Ley ‖ has shown that conversion of the erythrocytes from the discoid to the sickled and back to the discoid form may be reproduced in as many as five complete cycles without changing the osmotic or mechanical fragility of the cells. Previous observers have reported that the mechanical fragility of oxygenated red cells was normal in the anemia.[11] However, of the patients studied here, three of six showed marked elevation and one showed slight elevation of the mechanical fragility of oxygenated erythrocytes compared with the normal range of 3.0%±1 reported for the method by Emerson and co-workers.[7] Lange and associates,[11] using the method of Shen,[8] interpreted the results of six patients with anemia as normal. However, when these results are compared with the normal range established by Emerson for the same method it is seen that five of the patients had significantly elevated erythrocyte mechanical fragilities. None of the trait patients reported here had an abnormal increase in mechanical fragility of oxygenated red cells, and Lange's patients with trait showed only minimal changes. After sterile incubation for 24 hours, the blood of four patients with the anemia and of one with the trait showed abnormal elevation of mechanical fragility. These results are subject to much the same interpretations as are those of the osmotic fragility determinations made following sterile incubation.

The extreme fragility to mechanical trauma of the anemia cells while in the sickled form has been reported by Diggs and Bibb,[30] Shen and co-workers,[8] and Lange.[11] The studies by Lange were done contrasting the behavior of erythrocytes from patients with the anemia with those from patients with the trait under conditions in which the oxygen tension and hydrogen ion concentration were controlled. The changes in mechanical fragility were found to be directly related to the degree of sickling. The results as shown in Figure 9 and in close agreement with those reported previously. Thus, in the anemia the marked increases in erythrocyte mechanical fragilities take place in the physiologic range of oxygen unsaturation of venous blood; in the trait the changes take place only at oxygen saturations produced by artificial laboratory conditions.

COMMENT

Biophysics of the Sickling Phenomenon

In a previous paper of this series [4] some of the basic mechanisms of the sickling process were outlined and the phenomenon was shown to be dependent upon molecular orientation of the intracellular hemoglobin. In brief, it was demonstrated that, in hemoglobin solutions of concentrations comparable to intracellular conditions, the abnormal hemoglobin S molecules undergo alignment and parallel aggregation following deoxygenation to form birefringent hemoglobin tactoids. Consequently, the conclusion was reached that in all probability the birefringent sickled cell is a membrane-covered hemoglobin tactoid. On the basis of observations concerning the abnormally low solubility of reduced hemoglobin S and the similar orientation of the heme moieties in both the intact sickled cell and crystallized hemoglobin S, Perutz [32] has proposed that in the sickled erythrocyte the hemoglobin has crystallized out of solution, thereby disturbing the cell shape. Tosteson and co-workers [34] have reported that the change of water content on deoxygenation of the sickle cell is only from 64.1% to 63.4%, or a net loss of less than 1%. Thus, it seems improbable that actual crystallization of the intracellular hemoglobin takes place, since red cells contain approximately 34% hemoglobin, whereas crystals contain between 50% and 60%. Thus, to permit crystallization a loss of water much greater than 1% would be required. The water content of the tactoid is, however, considerably greater than that of a crystal, and so with intracellular tactoid formation only a small exchange of water would be expected. In addition, Rebuck and co-workers ¶ have shown by electron micro-

‖ Ley, A. B.: Personal communication to the authors.

scopy of the sickling process that there first occurs, on deoxygenation, irregular massing and aggregation of the hemoglobin at one side of the cell and that long chains of hemoglobin later form elongated fibers and rods in a three-dimensional framework. Cellular configurations of hemoglobin tactoids were found in which the spindle-shaped orientation was "somewhat compromised by forces inherent in the cellular ultrastructure." The methods of Bessis # have demonstrated the appearance of orderly striations on the cell surface oriented toward the spicules. The striations are further described as little rods (*petits batonnets*) of hemoglobin arranged in parallel fashion. Finally, Ponder * has found that, upon compression, sickle cells develop almost as much heat as do normal red cells or hemoglobin solutions, whereas much less heat is developed if paracrystalline cells are compressed. Most conclusive of all, Ponder has shown that x-ray-scattering studies do not give any evidence for crystalline structure in the sickled cell.

Although (according to Sydenstricker,[43] Rebuck,[36] Kass,† and Griggs and Harris ‡) there is evidence that factors in addition to hemoglobin S significantly affect the sickling process, it would seem that molecular orientation and hemoglobin tactoid formation are basic to the structural mechanism of the sickling process.

Of the various normal and abnormal hemoglobins tested, only hemoglobin S undergoes molecular aggregation and the gelling phenomenon.[44] Because of variations in the interaction of hemoglobin S with its companion intracellular pigment hemoglobin A, C, or F, etc.,[44] it is not possible to state that the ease with which sickling can be induced is determined solely by the concentrations of intracellular reduced hemoglobin S. Nevertheless, it has been demonstrated that relative to oxygen tensions or oxygen saturations of hemoglobin, the erythrocyte of sickle-cell anemia (75% to 100% hemoglobin S) sickles much more readily than does the trait erythrocyte (24% to 45% hemoglobin S) and that cells from patients with sickle-cell-hemoglobin-C disease (about 50% hemoglobin S) and sickle-cell-thalassemia disease (67% to 82% hemoglobin S) sickle with intermediate ease.§ Similarly, the oxygen tension at which tactoid formation can be induced in solutions of various combinations of hemoglobin S with hemoglobin A, C, or F or the hemoglobin present in thalassemia correlates closely with the tension of oxygen at which sickling can be induced in the intact cell.[13] There is, therefore, a rough correlation between the amount of hemoglobin S present in a cell and the oxygen tension at which tactoid formation and sickling can be induced.

The physiologic consequences of these observations in terms of the anemia and trait are that the sickling changes take place in the range of physiologic oxygen tensions for the anemia erythrocytes; not so for the trait erythrocytes, for these can only be made to change shape well below the physiologic range of capillary oxygen tensions. Similarly, the mechanical fragility of the erythrocytes from patients with the sickling anomaly varies with the oxygen tension at which the test is performed—the number of cells destroyed in the standard trauma test correlating closely with the number of cells in the sickled form.[11] Here again, significant increases in the mechanical fragility of the anemia cells occur in the physiologic range of oxygen tensions, while no alterations take place for trait cells within this range. It would seem inescapable that these cellular alterations follow directly from the observed behavior of the abnormal hemoglobin in the cell.

Intercellular Consequences of the Sickling Phenomenon

The intercellular effects of the basic abnormality are strikingly seen in the increases of whole blood viscosity observed in vitro

¶ References 35-38.

References 39-42.

* References 59 and 60 and Ponder, E.: Personal communication to the authors.

† Kass, E. H., and others: To be published.

‡ To be published.

§ References 13 and 45.

as the oxygen tension is progressively decreased. Artificial mixtures of sickle and normal cells demonstrate a straight-line relationship between the viscosity increase and the number of cells in the sickled form.[18] Since viscosity changes develop from variations in the internal friction of a suspension, in this special instance the entangling and enmeshing of the distorted erythrocytes appear adequate to explain the variations seen relative to oxygen tension. Although unlikely, it is possible that in the deoxygenated state the intermolecular attractive forces that lead to polymerization of the hemoglobin molecules are exerted across the cell membrane (distorted and thinned), binding the cells together.

The in vitro observations discussed here concerning the cellular and intercellular effects follow as a consequence of the unique behavior of the abnormal hemoglobin molecule; moreover, the quantitative changes bear a rough correlation with the amount of hemoglobin S present.

When these in vitro observations are applied to the problems presented in pathophysiology of sickle-cell disease, it is at once apparent that the changes of sickling, mechanical fragility, and the whole blood viscosity could only be produced in sickle-cell-trait blood by exceeding the usual limits of physiologic oxygen tensions; the changes would therefore be expected to have no in vivo counterpart or relevance. By and large, sickle-cell trait is a benign asymptomatic disease that only under exceptional circumstances || results in significant pathology. Hematologically the patients show no anemia, no significant red cell abnormalities of osmotic or mechanical fragility, no irreversibly sickled cells, and no shortened red cell life span.

In striking contradistinction to this, patients with sickle-cell anemia exhibit a variety of clinical manifestations and continually show all the red cell abnormalities described above—increased osmotic and mechanical fragility, irreversibly sickled cells, and shortened cell life span. Even in the physiologic range of capillary oxygen tensions, the deoxygenation of the hemoglobin is sufficient to result in molecular orientation, shape distortion, and sickling. In organs of slow blood flow sufficient numbers of erythrocytes sickle to result in increased blood viscosity. This increase in viscosity would serve to impede the blood flow further, thereby triggering a vicious cycle in which increases in sickling due to continued demands of adjacent tissues for oxygen result in further deoxygenation and increased viscosity and in further slowing of the blood flow. Moreover, the decrease in pH attendant upon locally increased CO_2 tension or increase of lactic acid would facilitate unloading of oxygen by the hemoglobin and hence the sickling process.

The physiologic consequences of this vicious cycle would seem to be mainly threefold: (1) a mechanism whereby plugs or masses of sickled erythrocytes become solid enough to occlude vessels and result in the "thrombotic" episodes characteristic of the disease, (2) a mechanism whereby the red cells become very fragile in terms of mechanical trauma and consequently susceptible to augmented destruction by the motion of the circulation, and finally (3) a mechanism whereby erythrostasis can be effected and the cells consequently "conditioned" by lack of access to or as a result of tissue competition for sources of cell-maintaining energy (e. g., glucose) and so made ready for autolysis. The evidence for this third point is indirect in the material presented here and is based on the observation that the circulating erythrocytes in sickle-cell anemia are characterized by abnormal osmotic and mechanical fragilities and because some are in the irreversibly or permanently sickled forms. Since repeated cycles of shape changes from sickled to discoidal forms have been shown not to result in alterations of erythrocyte osmotic and mechanical fragility, the measured changes are presumed therefore to be mediated by in vivo biologic processes and not

|| References 25 and 57.

related directly to the previously described in vitro abnormalities.

Thus, the biologic process in vivo is considered to be selective erythrocyte sequestration and conditioning. It has been shown by Ham and Castle [23] that after sterile incubation of blood there is a very significant increase in erythrocyte osmotic and mechanical fragility. And it has been shown by Shen [8] that sterile incubation of cells in the sickled form for varying periods of time results in the production of a number of cells that are permanently or irreversibly sickled. Therefore, it seems probable that the presence of erythrocytes in the irreversibly sickled form and cells that are osmotically and mechanically fragile indicates that the process of selective sequestration and conditioning has been in operation in the patient with the anemia, changes that may be comparable to sterile incubation in vitro.

Considerable direct evidence to support this hypothesis has been reported by Weisman and co-workers,[46] who showed by studies done at the time of splenectomy that specific selective sequestration of the anemia erythrocytes does in fact take place. Accordingly, if in the immediate presplenectomy period sickle-cell anemia erythrocytes are transfused into a nonsickling patient or, conversely, normal cells are transfused into a patient with sickle-cell anemia, the spleen, in both instances, was found to contain at the time of operation a greater proportion of sickle-cell anemia erythrocytes than was found in the peripheral blood. Moreover, the cells that had been selectively concentrated in the spleen showed marked increases in osmotic fragility and in spheroidicity, presumably because of conditioning that resulted from stasis. In sharp contrast to this, it was also demonstrated that the trait erythrocytes did not undergo selective sequestration in the spleen nor increases in osmotic fragility. In addition, Lichtman ¶ has shown by needle puncture that in sickle-cell anemia the spleen pulp contains a large per cent of sickled forms and that a large proportion of these are irreversible sickled cells (a twofold to thirteenfold increase compared with that of the peripheral blood).

In many ways these findings are analogous to those of Emerson and co-workers [7] in hereditary spherocytosis, a disease in which the abnormally spheroidal cells are trapped in the spleen presumably because of an abnormal geometric characteristic, namely, increased thickness. In sickle-cell anemia, however, the geometric abnormality occurs only in the cells that sickle and, therefore, become trapped in the spleen (especially in childhood) and elsewhere throughout the vascular bed because of an increase in blood viscosity at physiologic oxygen tensions. The final mechanisms by which the trapped cells are destroyed is still obscure. Although there is lack of evidence of marked increases in intravascular hemolysis, the finding of Crosby # of significantly increased levels of free hemoglobin in the plasma of sickle-cell anemia makes it probable that intravascular destruction secondary to increased erythrocyte mechanical fragility takes place to some extent. Fragmentation of the brittle sickled cells has been observed both in vitro and in vivo in the spleen.[46] Also, the increase of osmotic fragility observed by Weisman and co-workers [46] following erythrostasis was of such magnitude that hemolysis by osmotic forces may account for the destruction of some of the red cells. And, finally, the concept of erythrolytic factors in tissue, proposed by many workers,* or the induced deficiency of cell-maintaining energy factors of Selwyn and Dacie [50] appears applicable to sickle-cell anemia, particularly because of evidence for capillary thrombosis with prolonged stasis.

Evidence that the cellular and whole blood changes described here do have in vivo counterparts and physiologic relevance is pro-

¶ Lichtman, H.; Shapiro, H.; Ginsberg, V., and Watson, J.: Splenic Hyperfunction in Sickle Cell Anemia, read before the National Meeting of the American Federation for Clinical Research, Atlantic City, N. J., May 4, 1952.

References 47 and 48.

* References 49 and 50.

vided by the studies of Kass and co-workers,* who showed that a hematologic remission could be induced in sickle-cell anemia by prolonged corticotropin (ACTH) therapy. In this study with corticotropin therapy it was demonstrated that a decrease in the sickling of the red cells at physiologic oxygen tensions of gas mixtures occurred coincident with the following changes: a decrease in the whole blood viscosity corresponding to the decreased sickling, a decrease in the number of irreversibly or permanently sickled cells in the peripheral blood, a return to normal of the osmotic and mechanical fragilities, a fourfold decrease in the per cent of reticulocytes, and a fivefold decrease in the fecal urobilinogen.

CONCLUSIONS

Beginning with the genetically abnormal hemoglobin and extending to the hematologic findings, clinical manifestations, and pathologic changes, the following sequence of events appears adequate to explain some of the major aspects of the pathologic physiology of sickle-cell anemia. 1. The alignment and parallel orientation of the abnormal hemoglobin molecule in its insoluble deoxygenated state result in the formation of birefringent hemoglobin tactoids. Because of this intracellular molecular orientation, the normal biconcave disc form of the erythrocyte is distorted and the cell assumes the sickled form. The birefringent sickled erythrocyte is essentially a membrane-covered hemoglobin tactoid. 2. Owing entirely to the abnormal sickled form of the erythrocytes, the viscosity of the whole blood and the mechanical fragility of the erythrocytes are significantly increased at decreased oxygen tensions. With the increase in viscosity of the whole blood, a cycle is initiated in which the factors of stasis, lowered pH, and continuing tissue oxygen uptake combine to augment the number of sickled cells and prolong the stasis. 3. When red cells after stasis are again released into free circulation, a certain proportion have been fixed in the irreversibly sickled form and have also become increased in osmotic and mechanical fragilities as a result of such stasis. 4. The operation of this cycle appears to explain in large part the clinical manifestations of the disease, i. e., the abnormalities of the erythrocytes are responsible not only for the multiple vascular occlusive phenomena and venous thromboses that underly the tissue changes but also for the hemolytic anemia. 5. In the homozygous state the erythrocytes contain sufficient abnormal hemoglobin to allow sickling to occcur within the physiologic range of oxygen tensions.

In the heterozygous state the clinical course is essentially benign because sickling, although possible with artificially low oxygen tensions in vitro, ordinarily fails to take place in vivo.

* References 51 and 52.

REFERENCES

1. Callender, S. T. E.; Nickel, J. F., and Moore, C. V.: Sickle Cell Disease: Studied by Measuring the Survival Time of Transfused Red Blood Cells, J. Lab. & Clin. Med. **34**:90, 1949.

2. Singer, K.; Robin, S.; King, J. C., and Jefferson, R. N.: The Life Span of the Sickle Cell and the Pathogenesis of Sickle Cell Anemia, J. Lab. & Clin. Med. **33**:975, 1948.

3. Pauling, L.; Itano, H. A.; Singer, S. J., and Wells, I. C.: Sickle Cell Anemia: A Molecular Disease, Science **110**:543, 1949.

4. Harris, J. W.: Studies on the Destruction of Red Blood Cells: VIII. Molecular Orientation in Sickle Cell Hemoglobin Solutions, Proc. Soc. Exper. Biol. & Med. **75**:197, 1950.

5. Ham, T. H.: A Syllabus of Laboratory Examinations in Clinical Diagnosis, Cambridge, Mass., Harvard University Press, 1950.

6. Daland, G. A., and Castle, W. B.: A Simple and Rapid Method for Demonstrating Sickling of the Red Blood Cells: The Use of Reducing Agents, J. Lab. & Clin. Med. **33**:1082, 1948.

7. Emerson, C. P.; Shen, S. C.; Ham, T. H.; Fleming, E. M., and Castle W. B.: Studies on the Destruction of Red Blood Cells: IX. Quantitative Methods for Determining the Osmotic and Mechanical Fragility of Red Cells in the Peripheral Blood and Splenic Pulp; The Mechanism of Increased Hemolysis in Hereditary Spherocytosis (Congenital Hemolytic Jaundice) as Related to the Functions of the Spleen, A. M. A. Arch. Int. Med., to be published.

8. Shen, S. C.; Castle, W. B., and Fleming, E. M.: Experimental and Clinical Observations on Increased Mechanical Fragility of Erythrocytes, Science **100**:387, 1944.

9. Findlay, A.: Physical Chemistry for Students of Medicine, London, Longmans, Green & Co., 1924.

10. Van Slyke, D. D., and Sendroy, J., Jr.: Manometric Analysis of Gas Mixtures, J. Biol. Chem. **95**:509, 1932.

11. Lange, R. D.; Minnich, V., and Moore, C. V.: Effect of Oxygen Tension and of pH on the Sickling and Mechanical Fragility of Erythrocytes from Patients with Sickle Cell Anemia and the Sickle Cell Trait, J. Lab. & Clin. Med. **37**:789, 1951.

12. Neel, J. V.: The Inheritance of the Sickling Phenomenon, with Particular Reference to Sickle Cell Disease, Blood **6**:389, 1941.

13. Griggs, R. C., and Harris, J. W.: The Biophysics of the Variants of Sickle Cell Disease, J. Clin. Invest. **34**:937, 1955.

14. Wintrobe, M. M.: Clinical Hematology, Philadelphia, Lea & Febiger, 1952.

15. Milam, D. F., and Muench, H.: Hemoglobin Levels in Specific Race, Age and Sex Groups of a Normal North Carolina Population, J. Lab. & Clin. Med. **31**:878, 1946.

16. Shen, S. C.; Fleming, E. M., and Castle, W. B.: Studies on the Destruction of Red Blood Cells: V. Irreversibly Sickled Erythrocytes; Their Experimental Production in Vitro, Blood **4**:498, 1949.

17. Murphy, R. C., and Shapiro, S.: Sickle Cell Disease: I. Observations on Behavior of Erythrocytes in Sickle Cell Disease, Arch. Int. Med. **74**:28, 1944.

18. Sherman, I. J.: The Sickling Phenomenon, with Special Reference to Differentiation of Sickle Cell Anemia from the Sickle Cell Trait, Bull. Johns Hopkins Hosp. **67**:309, 1940.

19. Hahn, E. V., and Gillespie, E. B.: Sickle Cell Anemia: Report of a Case Greatly Improved by Splenectomy, Arch. Int. Med. **39**:233, 1927.

20. Scriver, J. B., and Waugh, J. R.: Studies on a Case of Sickle Cell Anemia, Canad. M. A. J. **23**: 2375, 1930.

21. Nygaard, K. K.; Wilder, M., and Berkson, J.: The Relation Between Viscosity of the Blood and the Relative Volume of Erythrocytes (Hematocrit Value), Am. J. Physiol. **114**:128, 1935.

22. Glaser, O.: Medical Physics, Chicago, The Year Book Publishers, Inc., 1950, Vol. 2.

23. Ham, T. H., and Castle, W. B.: Relation of Increased Hypotonic Fragility and of Erythrostasis to the Mechanism of Hemolysis in Certain Anemias, Tr. A. Am. Physicians **55**:127, 1940.

24. Singer, K., and Fisher, B.: Studies on Abnormal Hemoglobins: V. The Distribution of Type S (Sickle Cell) Hemoglobin Within the Red Cell Population in Sickle Cell Anemia, Blood **7**:1216, 1952.

25. Margoleis, M. P.: Sickle Cell Anemia, A Composite Study and Survey, Medicine **30**:357, 1951.

26. Ham, T. H., and Castle, W. B.: Relation of Increased Hypotonic Fragility and Erythrostasis to the Mechanism of Hemolysis in Certain Anemias, Proc. Am. Philosoph. Soc. **82**:411, 1940.

27. Castle, W. B., and Daland, G. A.: Susceptibility of Mammalian Erythrocytes to Hemolysis with Hypotonic Solutions, Arch. Int. Med. **60**:949, 1937.

28. Sharpsteen, J. R.: Physio-Chemical Mechanisms in the Pathogenesis of Certain Hemolytic Anemias, Am. J. M. Sc. **229**:506, 1955.

29. Guest, G. M.: Osmometric Behavior of Normal and Abnormal Human Erythrocytes, Blood **3**: 541, 1948.

30. Diggs, L. W., and Bibb, J.: The Erythrocyte in Sickle Cell Anemia, J. A. M. A. **112**:695, 1939.

31. Perutz, M. F., and Mitchison, J. M.: State of Haemoglobin in Sickle-Cell Anemia, Nature, London **166**:677, 1950.

32. Perutz, M. F.; Liquori, A. M., and Eirich, F.: X-Ray and Solubility Studies of the Haemoglobin of Sickle-Cell Anaemia Patients, Nature, London **167**:929, 1951.

33. Tosteson, D. C.: Red Cell Potassium Exchange in Sickle Cell Anemia, New York, Brookhaven National Laboratory (BNL-1086) and College of Physicians and Surgeons, (nd).

34. Tosteson, D. C.; Shea, E., and Darling, R. C.: Potassium and Sodium of Red Blood Cells in Sickle Cell Anemia, J. Clin. Invest. **31**:406, 1952.

35. Rebuck, J. W.; Sturrock, R. M., and Monto, R. W.: Further Evidence of Intracorpuscular Paracrystallization of Hemoglobin in Sickle Cells, Anat. Rec. **109**:340, 1951.

36. Rebuck, J. W.; Monto, R. W., and Sturrock, R. M.: The Structural Basis of Sickling and Its Electron Microscopy, Am. J. Path. **28**:530, 1952.

37. Rebuck, J. W.; Sturrock, R. M., and Monto, R. W.: Electron Microscopy of the Sickling Process, Henry Ford Hosp. M. Bull. **1**:29, 1953.

38. Rebuck, J. W., and Sturrock, R. M.: The Tridimensional Nature of the Sickling Process, Anat. Rec. **115**:362, 1953.

39. Bessis, M.; Bricka, M., and Breton-Gorius, J.: Examen de la surface des érythrocytes falciformes au microscope électronique, Compt. rend. Acad. sc. **235**:143, 1952.

40. Bessis, M.; Bricka, M., and Breton-Gorius, J.: Differents Aspects de la surface des érythrocytes falciformes observés au microscope électronique, Rev. hémat. **8**:222, 1953.

41. Bessis, M.; Bricka, M.; Breton-Gorius, J., and Tabuis, J.: Les Formes myéliniques et l'agglutination des érythrocytes falciformes, Compt. rend. Acad. Sc. **236**:1206, 1953.

42. Bessis, M.; Bricka, M., and Breton-Gorius, J.: Différents aspects de la surface des érythrocytes falciformes observés au microscope électronique, Rev. hémat. **8**:222, 1953.

43. Sydenstricker, V. P.; Mulherin, W. A., and Hanseel, R. W.: Sickle Cell Anemia: Report of Two Cases in Children, with Necropsy in One Case, Am. J. Dis. Child. **26**:132, 1932.

44. Singer, K., and Singer, L.: Studies on Abnormal Hemoglobins: VIII. The Gelling Phenomenon of Sickle Cell Hemoglobin; Its Biologic and Diagnostic Significance, Blood **8**:1008, 1953.

45. Motulsky, A.; Paul, M. H., and Durrum, E. L.: Paper Electrophoresis of Abnormal Hemoglobins and Its Clinical Applications, Blood **9**:897, 1954.

46. Weisman, R., Jr.; Hurley, T. H.; Harris, J. W., and Ham, T. H.: Studies on the Function of the Spleen in the Hemolysis of Red Cells in Hereditary Spherocytosis and Sickle Cell Disorders, J. Lab. & Clin. Med. **42**:965, 1954.

47. Crosby, W. H.: The Significance of Hemoglobinemia and Associated Hemosiderinuria, with Particular Reference to Various Types of Hemolytic Anemias, J. Lab. & Clin. Med. **38**:829, 1951.

48. Crosby, W. H.: The Metabolism of Hemoglobin and Bile Pigment in Hemolytic Disease, Am. J. Med. **18**:112, 1955.

49. Ponder, E.: Analytical Review: Certain Hemolytic Mechanisms in Hemolytic Anemia, Blood **6**:559, 1951.

50. Castle, W. B.; Ham, T. H., and Shen, S. C.: Observations on the Mechanism of Hemolytic Transfusion Reactions Occurring Without Demonstrable Hemolysin, Tr. A. Am. Physicians **63**:161, 1950.

51. Kass, E. H.; Geiman, Q. M.; Ingbar, S. H.; Ley, A. B.; Harris, J. W., and Finland, M.: Some Diseases Which May Be Activated by ACTH: Observations on Sickle Cell Anemia and Malaria, in Proceedings of the Second Clinical ACTH Conference, edited by J. R. Mote, Philadelphia, The Blakiston Company, 1951, Vol. 2, Therapeutics, p. 376.

52. Kass, E. H.; Ingbar, S. H.; Harris, J. W., and Ley, A. B.: Chemical Abnormalities in the Erythrocytes in Sickle Cell Anemia, Their Relationship to Sulfhydryl Metabolism and the Effects of ACTH, J. Clin. Invest. **30**:652, 1951.

53. McCord, W. M.; Kelley, W. H.; Switzer, P. K., and Culp, F. B.: Viscosity Studies of Erythrocytes from Persons with Sickle Cell Disease, Proc. Soc. Exper. Biol. & Med. **69**:19, 1948.

54. Bauer, J.: Sickle Cell Disease: Pathogenic, Clinical and Therapeutic Considerations, Arch. Surg. **41**:1344, 1940.

55. Greenberg, M. S., and Kass, E. H.: Correlation of in Vitro Studies of Blood with Clinical Observations in Patients with the Sickling Phenomenon, Clin. Res. Proc. **3**:96, 1955.

56. Selwyn, J. G., and Dacie, J. V.: Autohemolysis and Other Changes Resulting from the Incubation in Vitro of Red Cells from Patients with Congenital Hemolytic Anemia, Blood **9**:414, 1954.

57. Smith, E. W., and Conley, C. L.: Sicklemia and Infarction of the Spleen During Airplane Flight, Bull. Johns Hopkins Hosp. **96**:35, 1955.

58. Branson, H., and Banks, L. O.: The Turnover Time of Phosphorus in Normal, Sickle Trait and Sickle Cell Anemia Blood in Vitro, Measured with P^{32}, Science **115**:89, 1952.

59. Ponder, E.: The Specific Heat and the Heat of Compression of Human Red Cells, Sickled Red Cells, and Paracrystalline Rat Red Cells, J. Gen. Physiol. **38**:575, 1955.

60. Dervichian, D. G.; Fournet, G.; Guinier, A., and Ponder, E.: Structure Submicroscopique des globules rouges contenant des hemoglobines abnormales, Rev. hémat. **7**:567, 1952.

On Myelofibrosis

DONALD R. KORST, M.D.
DALLAS V. CLATANOFF, M.D.
and
ROBERT F. SCHILLING, M.D., Madison, Wis.

A condition with fibrosis of the bone marrow, extramedullary hemopoiesis, and splenic enlargement was described one-half century ago. Its close relationship to chronic granulocytic leukemia and polycythemia rubra vera or its classification as a separate entity has stimulated much interest. In 1871 Wood [1] wrote of a "splenic variety of pseudoleukemia or splenic cachexia" and speculated as to whether there was any consistent change in the bone marrow. He described cases of splenomegaly associated with gelatinous degeneration of the bone marrow. Heuck [2] is credited with an early case report associating generalized osteosclerosis, hepatosplenomegaly, and anemia. In several extensive reviews Sippy * described splenic pseudoleukemia as a condition closely associated with leukemia and having as common findings splenomegaly, anemia, lack of lymphadenopathy, and a slowly progressive course. He described a case of pseudoleukemia with foci of marrow cells surrounded by connective tissue. Later the terms myelosclerosis and osteosclerosis † with aleukemic myelosis were applied to this syndrome and the marrow changes were described as a diffuse increase of connective tissue and trabeculae. These were sternal biopsy impressions, and the sections, in addition to fibrosis, showed megakaryocytosis and foci of myeloid elements. Myelofibrosis was a term applied and associated with a leukemoid blood picture by Mettier and Rusk [7] in 1937. Some of the patients with leukoerythroblastic anemia observed by Vaughan and Harrison ‡ were found to have myelosclerosis. They thought that polycythemia, leukemia, and myelosclerosis were a closely related group of diseases. A recently expressed view [10] is that myeloid metaplasia and myelosclerosis are now commoner than formerly.

The purpose of this paper is to describe the clinical and laboratory findings in 23 patients who had myelofibrosis established by biopsy or autopsy. In 21 cases the diagnosis was established by biopsy before death. No patient known to have metastatic carcinoma or tuberculosis is included, and in only 1 of the 23 patients was there a history of exposure to marrow toxins (Case 17). The case summaries of all of the patients are condensed and presented in Table 1.

A syndrome of a variable degree of pallor, splenomegaly, leukemoid blood picture, variation in erythrocyte morphology, circulating nucleated red cells, variable platelet levels, hypocellular bone marrow aspiration, and extramedullary hemopoiesis is associated with myelofibrosis. This definition, which is essentially that of Dameshek,§ would aptly describe the cases reported here. In addition, we would like to emphasize the occurrence of circulating megakaryocyte fragments, tissue megakaryocytosis, increased hemolysis, and hyperuricemia in cases of myelofibrosis. Many names, in addition to those mentioned,

Submitted for publication July 25, 1955.

Department of Medicine, University of Wisconsin Medical School; Trainee, National Cancer Institute (Dr. Clatanoff).

Supported in part by funds from the Wisconsin Alumni Research Foundation and an Institutional Grant (INSTR — 71) from the American Cancer Society to the University of Wisconsin.

* References 3 and 4.

† References 5 and 6.

‡ References 8 and 9.

§ References 10 and 11.

TABLE 1.—*Case Summaries*

Case	Age, Yr.	Sex	Clinical Features	Physical Examination			Admitting Diagnosis	Present or Final Diagnosis	Duration of Disease, Yr., and Status
				Spleen*	Liver*	Nodes			
1	60	F	Weakness and splenomegaly 5 mo.; 22 lb. weight loss; son died age 35 with splenomegaly; sternal tenderness	20	8	0	Myelofibrosis	Unchanged	1½ Alive
2	61	F	Urinary calculi 10 yr.; gout 2 yr.; "blood count too high 5 yr. ago"; uncomfortably large spleen, wt. loss, easy bruising; positive tourniquet test	17	5	0	Myelofibrosis and leukemia,† gout	Unchanged	5-7 Alive
3	65	M	Weakness, dyspnea, fullness left side for 9 mo.; sternal tenderness	14	7	0	Leukemia and myelofibrosis	Myelofibrosis, hemolytic anemia	2 Died at home
4	57	M	Weakness and fatigue 1 yr.; anemia and transfusions 2 mo.; positive tourniquet test and sternal tenderness	20	4	0	Myelofibrosis, hemolytic anemia	Myelofibrosis, myeloid metaplasia,‡ leukemic blood picture	1¾ Alive
5	66	F	Tumor in abdomen 6 mo., with weight loss and anemia; sternal tenderness	14	4	0	Polycythemia	Myelofibrosis, myeloid metaplasia	2½ Autopsy
6	70	F	Lung abscess; anemia 15 yr. and leukemia 10 yr.; sternal tenderness	15	5	0	Leukemia, lung abscess	Myelofibrosis, myeloid metaplasia	10 Autopsy
7	63	M	Pseudoxanthoma elasticum and purpura 22 yr.; polycythemia 10 yr.; anemia 2 yr.	7	6	0	Polycythemia	Myelofibrosis, hemolytic anemia	22 Alive
8	21	M	Abdominal swelling, weakness and wt. loss for 3 mo.; 50 transfusions one year	17	3	0	Myelofibrosis, hemolytic anemia	Unchanged, myeloid metaplasia	4 Died at home
9	59	M	Abdominal mass and ankle joint pain for 4 mo.	22	5	§	Leukemia	Myelofibrosis, gout	7 Alive
10	44	M	Fullness in lt. abdomen 3 yr.; need for transfusions; leukemia cutis by biopsy; sternal tenderness	11	8	‖	Leukemia	Myelofibrosis, leukemia, hemolytic anemia, myeloid metaplasia	1½ Autopsy
11	52	F	Weakness and fullness in lt. abdomen for 1 yr.; sternal tenderness	24	8	0	Leukemia and myelofibrosis	Unchanged	1 Alive
12	64	F	Anemia 5 yr. and weakness 1 yr.; splenomegaly 2 yr.; sternal tenderness	10	8	0	Myelofibrosis	Unchanged	8½ Alive
13	72	M	Wt. loss and abdominal tumor for 8 mo.; sternal tenderness; 34 transfusions one year	14	8	§	Leukemia	Myelofirosis, myeloid metaplasia (spleen biopsy)	2½ Died at home
14	73	M	Tired for 3 mo.; no response to liver and iron therapy of anemia; weekly transfusions	16	7	0	Leukemia and myelofibrosis	Unchanged	1½ Alive
15	61	M	Tired 2 yr.; anemia requiring 12 transfusions	15	3	§	Myelofibrosis	Unchanged, coronary thrombosis	2½ Died at home
16	54	M	Mass in abdomen 4 mo.; "leukemia" for 2 yr.	17	11	0	Leukemia	Myelofibrosis, myeloid metaplasia	4 Autopsy
17	47	M	Weakness, gastrointestinal bleeding several mo.; worked in paint shop	6	3	0	Polycythemia	Polycythemia, myeloid metaplasia, myelofibrosis	7 Autopsy
18	50	F	Anemia 7 yr. ago; splenectomy (1630 gm.) 5 yr. ago; weakness and cont. anemia	..	15	‖	Myelofibrosis	Myelofibrosis, myeloid metaplasia	8 Died at home
19	61	M	Anemia several mo.; gastric resection 2 mo. before for suspected bleeding ulcer	2	4	0	Myelofibrosis	Unchanged	1½ Died at home
20	47	F	Weakness and wt. loss for 1 yr.; splenomegaly noted at hysterectomy 4 yr. ago; sternal tenderness	21	12	0	Myelofibrosis	Unchanged	2¼ No information
21	46	M	Swelling in abdomen for a year	3	15	0	Polycythemia	Myelofibrosis, myeloid metaplasia	2¼ Died at home
22	45	M	Weakness and lump in lt. side 6 mo.; silicosis for 7 yr.	12	5	0	Silicosis	Silicosis, myelofibrosis	1+ No information
23	68	M	Weakness and anemia for 2 yr.	4	4	§	Myelofibrosis	Unchanged	2+ No information

* Centimeters below the costal margin.

† Chronic granulocytic leukemia.

‡ Myeloid metaplasia is listed as being present only if demonstrated histologically.

§ Small palpable nodes in one or two areas.

‖ General lymphadenopathy.

TABLE 2.—*Blood Description at Time of Biopsy Diagnosis of Myelofibrosis*

Case	Hemoglobin, Gm./100 Ml.	WBC, 1000/Cu. Mm.	Description of Leucocytes	Nucleated RBC, %	Reticulocytes, %	Platelets and Megakaryocyte Fragments	Erythrocyte Morphology
1	12.3	14.0	Leukemoid*	2.7	5.8	Normal 3 meg. frag.	Poikilocytes (teardrop forms), marked variation
2	14.2	51.0	Leukemoid, 1% blasts	1.0	5.4	Increased 3 meg. frag.	Marked variation, teardrop forms
3	10.4	28.5	Leukemoid, 0.5% blasts	0.5	3.3	Normal 1 meg. frag.	Marked variation, teardrop forms
4	3.4	7.7	Myeloid 69%; 2.6% blasts	9.0	5.4	Decreased 1 meg. frag.	Hypochromic, teardrop forms
5	10.8	112.5	Leukemoid, 2.6% blasts	10.6	4.1	Normal 10 meg. frag.	Marked variation, teardrop forms
6	8.8	27.1	Leukemoid, 0.9% blasts	0.2	4.4	Increased size 1 meg. frag.	Marked variation, teardrop forms
7	7.1	4.2	Normal differential count	1.0	8.4	Increased, in clumps	Variation, teardrop forms
8	8.4	5.2	Leukemoid, 1.2% blasts	13.6	6.2	Normal with atypical forms 2 meg. frag.	Variation, teardrop forms
9	11.5	9.0	Leukemoid, 0.6% blasts	8.6	1.9	Increased, in clumps	Marked variation, teardrop forms
10	8.5	6.6	Leukemoid	4.8	6.4	Increased, in clumps, 10 meg. frag.	Variation, teardrop forms
11	7.3	232.0	Leukemoid, 8.4% blasts	1.8	5.8	Increased, in clumps 14 meg. frag.	Slight variation, hypochromia
12	8.1	7.3	Leukemoid, 0.8% blasts	2.6	2.7	Decreased	Rouleaux, variation, teardrop forms
13	10.8	13.7	Leukemoid, 0.2% blasts	5.0	5.4	Increased atypical forms	Variation, teardrop forms
14	6.3	8.5	Leukemoid	1.6	3.9	Markedly increased, in clumps 2 meg. frag.	Hypochromia, variation, teardrop forms
15	9.4	9.7	Normal, 4% immature granulocytes	0	1.7	Low normal 1 meg. frag.	Moderate variation with teardrop forms
16	11.0	32.4	Leukemoid, 1.0% blasts	0.2	2.0	Increased 6 meg. frag.	Variation, teardrop forms
17	8.6	13.3	Leukemoid, 1.2% blasts	0.5	6.9	Increased, atypical forms meg. frag. seen	Slight variation
18	8.4	71.6	Leukemoid, 1.6% blasts	28.0	7.2	Decreased, large forms	Hypochromia, variation, teardrop forms
19	4.8	1.9	Normal, 0.2% blasts	0.4	4.0	Normal, atypical forms 2 meg. frag.	Marked variation
20	6.8	2.8	Normal, 0.8% blasts	2.4	0.5	Low, large forms	Marked variation, teardrop forms
21	16.3	19.9	Leukemoid	0.4	2.0	Increased 3 meg. frag.	Some variation
22	15.0	31.7	Leukemoid	0.2	2.9	Increased	Slight size variation
23	4.4	3.2	Normal, 0.2% blasts	6.0	4.0	Decreased, atypical forms	Some variation, teardrop forms

* Leukemoid here includes those patients in whom original diagnosis was thought to be leukemia.

have been applied to this syndrome and are well reviewed in the literature.|| A further attempt to review the literature will not be made, as such reviews are available in a number of papers published since 1933.¶ The purpose of this paper is to stress the close relationship of myelofibrosis to chronic granulocytic leukemia and polycythemia vera and to show that at certain stages in these diseases their separation into distinct entities may be difficult or impossible. Case summaries are presented in Table 1, and the hematologic studies are presented in Table 2. Results of marrow aspiration, marrow biopsy, and x-rays are presented in Table 3, and special studies are presented in Table 4.

|| References 11-18.

¶ References 5, 6, 8, 12, 14, 15, and 18-23.

TABLE 3.—*Special Studies Done at the Time of Diagnosis of Myelofibrosis*

Case	Marrow Aspiration	Fixed Marrow Section, Biopsy or Autopsy	Bone X-Rays
1	Dry tap, sternum	Myelofibrosis with remaining hemopoietic foci	Femora and ribs normal
2	Dry tap, sternum	Myeloid hyperplasia and foci of myelofibrosis	Femora, ribs and pelvis: osteosclerosis
3	Sinus blood, sternum	Marrow showing some myelofibrosis	Pelvis, ribs, femora: normal
4	Sinus blood, sternum	Myelofibrosis with patchy hyperplastic foci of myelopoiesis	Right femur and ribs: osteosclerosis
5	4 dry taps, sternum, ilium	Myelofibrosis; several foci of myelopoiesis	One femur normal
6	Only 2 particles, sternum	Myelofibrosis; residual foci of myelopoiesis	Ribs, long bones: osteosclerosis
7	Ilium, sinus blood; rich marrow particles from sternum	Myelofibrosis with no areas of normal marrow	Spine: osteosclerosis
8	Not done	Myelofirosis; osteosclerosis, hypocellular	Ribs, scapulae, long bones, clavicles: osteosclerosis
9	Sinus blood, sternum	Hypocellular, megakaryocytosis, myelofibrosis	Spine and pelvis: osteosclerosis
10	3 dry taps, sternum	Myelofibrosis, some myelopoiesis remaining	Ribs, femora: osteosclerosis
11	2 dry, sternum; 2 dry, iliac; 1 sternal blood with small particle	Myeloid hyperplasia, patchy myelofibrosis, megakaryocytosis	Ribs, spine, pelvis, right femur: normal
12	Sinus blood, sternum	Cellular marrow with compact masses of fibrous tissue	Spine, pelvis: osteosclerosis
13	2 sternal, blood only	Myelofibrosis with hypocellular areas and increased megakaryocytes	Ribs, femora: normal
14	Sinus blood, sternum	Myelogenous leukemia with some myelofibrosis	Normal ribs
15	Dry tap, sternum	Osteosclerosis, myelofibrosis	Femora normal
16	2 sternal, blood only	Myelosclerosis with few myeloid cells	Ribs normal
17	4 dry taps, sternum	Rib, vertebra, sternum hyperplastic areas with increased megakaryocytes and fibrosis	Ribs, spine, long bone, pelvis: osteosclerosis
18	.....	Myelofibrosis, some myelopoiesis	Ribs, pelvis, femora: osteosclerosis
19	Sternum, blood only	Myelofibrosis with little cellularity	Ribs normal
20	.....	Myelofibrosis with some myelopoiesis	Long bones: diffuse osteosclerosis
21	Sternum, blood only	Hypoplastic marrow with myelofibrosis	.....
22	1 dry tap, sternum	Myelofibrosis with few myelopoietic foci	Long bones: normal
23	3 dry taps, sternum	Heavy fibrosis, myelopoietic centers, incr. megakaryocytes	Femora: normal

POLYCYTHEMIA AND MYELOFIBROSIS

Minot and Buckman [25] in 1923 described three patients with erythremia who developed anemia after 5, 18, and 20 years of observed splenomegaly. The development of an anemic phase of polycythemia associated with a sclerotic marrow has been documented.# This phase is sometimes referred to as "spent" or "static phase" of polycythemia.* Patients seen when the syndrome associated with myelofibrosis and myeloid metaplasia is predominant may give a history of previous polycythemia.† There does not seem to be any good evidence that fibrosis is secondary to therapy.[28] Four of the twenty-three patients here reported had mild polycythemia or polycythemia of a degree requiring therapy (Cases 5, 7, 17, and 21). A gradual change over a two- or three-year period is pictured in Figure 1.

TABLE 4.—*Other Studies Done at Time of Diagnosis of Myelofibrosis*

Case	Blood Uric Acid, Mg./100 Ml.	Fecal Urobilinogen, 4-Day Specimen, Mg./24 Hr.	Direct Coombs Test
1.....	10.6	431	Neg.
2.....	4.8	868 & 494	Neg.
3.....	7.5	419	Neg.
4.....	6.0	1571	Neg.
5.....	9.8	300	Neg.
6.....	18.4	68	Neg.
7.....	5.8	432	Neg.
8.....	4.6	762	Neg.
9.....	11.0	...	.....
10.....	....	152	.....
11.....	5.8	129	.....
12.....	....	290	.....
13.....	....	560	.....
14.....	3.8	168	Neg.

When first seen in this hospital Case 5 had a hemoglobin range from 14 to 17 gm/100 ml. and an erythrocyte count from 4,700,000 to 6,300,000/cu. mm., and the leucocytes numbered 23,000/cu. mm. Biopsy of the liver, spleen, and lymph nodes on this first admission revealed extramedullary hemopoiesis. Sternal marrow aspirations were dry, and biopsy of the marrow showed hyperplasia and was interpreted as consistent with the diagnosis of polycythemia or early chronic granulocytic leukemia. The patient

References 19 and 26-28.

* References 29 and 30.

† References 17 and 31.

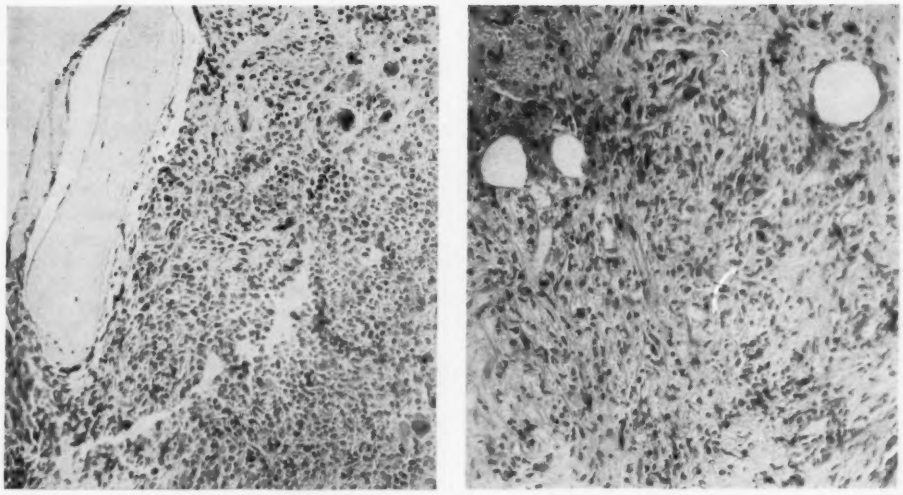
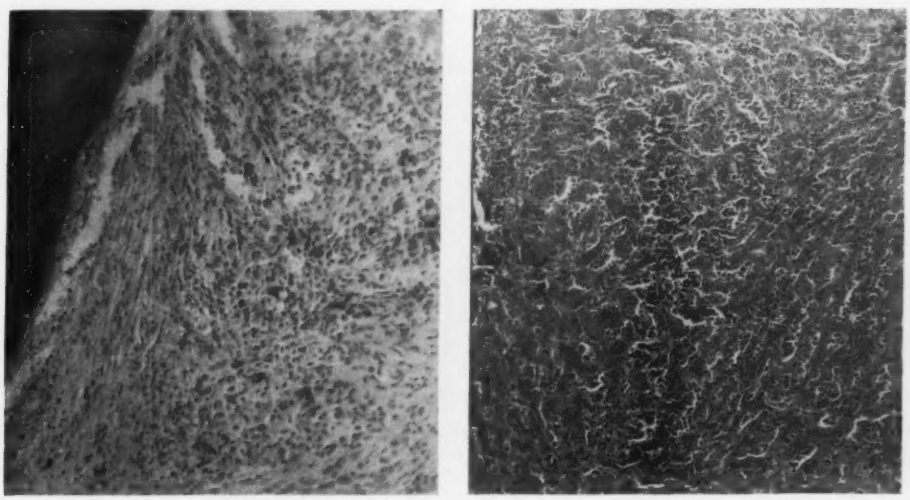


Fig. 1 (Case 5).—Clinical course of polycythemia with a change to myelofibrosis over a two-year period. Above: sternal marrow biopsy specimens. Left, hyperplastic marrow seen at onset of polycythemia; reduced from mag. × 150. Right, 15 months later, at a time of anemia and leucocytosis; extensive marrow fibrosis; reduced from mag. × 150. Below: postmortem sections 22 months after upper left biopsy and 7 months after the upper right biopsy. Left, vertebra showing myelofibrosis with patches of cellular marrow; reduced from mag. × 150. Right, liver with extramedullary hemopoiesis; reduced from mag. × 75.



was treated with radioactive phosphorus, which reduced the hemoglobin level, but the spleen continued to enlarge and she was troubled with splenic infarcts. Eight months after her first admission a repeat marrow biopsy showed hyperplastic marrow with minimal fibrotic activity, and the hemoglobin was 16.9 gm/100 ml. Twenty months after the first admission she was anemic, and at this time the marrow biopsy specimen revealed dense fibrosis. A postmortem examination confirmed extensive myelofibrosis with extramedullary hemopoiesis of the liver, spleen, lymph nodes, and kidney. Megakaryocytes were numerous in all tissues.

Case 17 was observed intermittently for 11 years before death. In 1935, at the time of his first hospital admission, the hemoglobin was 18 gm/100 ml. and the erythrocyte count was 7,500,000/cu. mm.; no therapy for polycythemia was given. In 1939 his hemoglobin level was 12 gm/100 ml. and the spleen was felt 6 cm. below the costal margin. The leuco-

cyte count was 18,000/cu. mm. The attending physicians believed that he had "spent" polycythemia. X-rays revealed osteosclerosis in 1944 (Fig. 4), and the hemoglobin was now 8.6 gm/100 ml. In the following year he was given roentgen therapy to the spleen, with some decrease in size of the organ. In 1946 his hemoglobin was 18 gm/100 ml.; the erythrocyte count was 6,800,000/cu. mm., and the leucocyte count was 18,000/cu. mm. He died soon after this, and autopy revealed a hyperplastic marrow with increased megakaryocytes and patches of myelofibrosis in the sternum, vertebrae, and ribs. Extramedullary hemopoiesis was found in the spleen, liver, lungs, kidneys, and adrenals. Sections of the femur showed a hypoplastic marrow with increased megakaryocytes (Fig. 4).

CHRONIC GRANULOCYTIC LEUKEMIA AND MYELOFIBROSIS

In studies of leukemia there is frequent mention of the incidence of myelofibrosis, and it has been stated that this is an end-stage of leukemia or that possibly the initial diagnosis should have been myelofibrosis rather than leukemia.‡ The fibrosis noted in the marrow often is intermixed with areas of hyperplastic marrow. Leukemia has been reported as a terminal event in myeloid metaplasia.[34] Patient 4 now has a leukemic blood picture one year after splenectomy for hemolytic anemia associated with myelofibrosis and myeloid metaplasia (Fig. 5). Five patients in this study were initially diagnosed and treated as having chronic granulocytic leukemia (Cases 6, 9, 10, 13, and 16). Four other patients (Cases 2, 3, 11, and 14) were initially thought to have both leukemia and myelofibrosis. Several of these patients later developed a more characteristic picture of myelofibrosis, as shown in Case 16.

The patient initially had a leucocyte count of 87,000/cu. mm., with mostly immature granulocytes and 5% blast cells. X-ray therapy to the spleen caused a fall in the leucocyte level, but there was no improvement in the hemoglobin level or symptomatology. There was little change in his clinical course during the next three-year period, at the end of which time a sternal biopsy revealed myelofibrosis. He died of pneumonia, and at autopsy leukemic infiltration of the organs was not found. The spleen, liver, and kidneys showed extensive extramedullary hemopoiesis, and specimens of sternum, ribs, and vertebrae showed increased thickness of bony trabeculae, replacement of much marrow by fibrous tissue and increased megakaryocytes.

The clinical course of Case 10 is also worthy of comment.

He initially was treated for one year for leukemia, with some symptomatic improvement and decrease in the size of the spleen even though attempted marrow aspirations yielded only dry taps. Osteosclerosis was noticed in the ribs on a routine chest x-ray, and myelofibrosis was proved by marrow biopsy one year later. Leukemia cutis was previously diagnosed by biopsy. The patient died 17 months after the onset of his illness, and at that time the hemoglobin was 8.5 gm/100 ml.; leucocytes numbered 42,000/cu. mm., with 29% myeloblasts. Postmortem examination revealed the sternal and vertebral marrow cavities to be replaced by dense yellowish fibrous tissue. The lymph nodes showed infiltration of myeloid cells, and the spleen revealed increased myeloid cells, many megakaryocytes, and areas of erythropoiesis.

REVIEW OF ALL TWENTY-THREE PATIENTS WITH MYELOFIBROSIS

Nine of the twenty-three patients in this report were initially diagnosed as having myelofibrosis, and the final impressions on all twenty-three patients included myelofibrosis. Of the entire group, the common feature was the finding of significant fibrosis of the bone marrow in biopsy or autopsy specimens. The age ranged from 21 to 73 years, and there were 8 women and 15 men. Weakness was noted in 16 patients, and abdominal tumor, in 13. Other symptoms consisted of pallor in nine, weight loss in five, dyspnea in four, ease of bleeding or easy bruising in three, gout in two, and a history of polycythemia in two patients. A review of all physical findings at the time when myelofibrosis was established revealed that splenomegaly and hepatomegaly were consistent findings (Table 1). The spleen was more than 7 cm. below the costal margin in 19 patients. Palpation for lymph node enlargement was made in all cases, and the nodes were reported to be insignificant in 18 of the patients and questionably significant in the other 5. Definite sternal tenderness was noted in 10 cases and found to be absent

‡ References 12, 32, and 33.

in 13 of the cases. In general, the duration of the symptoms prior to diagnosis was long, being 2 to 120 months before the diagnosis of myelofibrosis was established. Splenomegaly without other definite symptoms often existed for many months before a diagnosis was established.

Laboratory studies, in addition to those shown in Tables 2, 3, and 4, revealed normal osmotic fragility of red cells in 12 patients. The basal metabolic rate in eight patients ranged from +20% to +83%, with an average of +40%. In 19 patients a marrow aspiration yielded a dry tap or sinus blood.

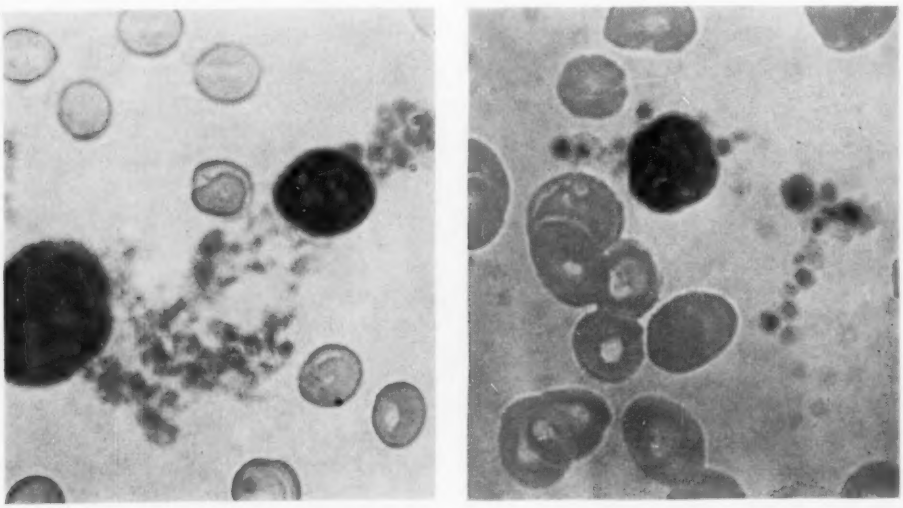
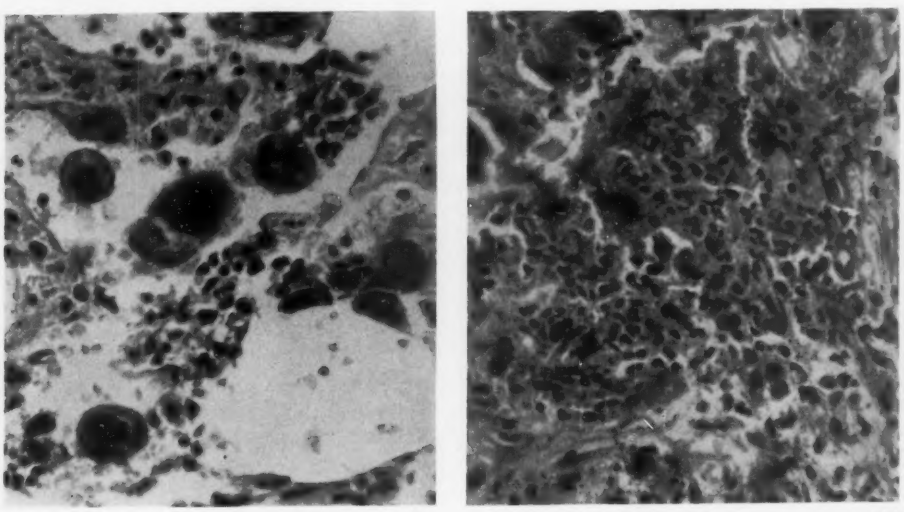


Fig. 2.—Above: megakaryocyte fragments and clumps of platelets including large abnormal forms from peripheral blood smears. Left, Case 2; right, Case 14; both reduced from mag. × 1900. Below: sternal marrow biopsy specimens. Left, Case 9, showing hypocellular fibrotic marrow and increased megakaryocytes; reduced from mag. × 300. Right, Case 14, showing a hyperplastic marrow with areas of fibrosis and increased megakaryocytes; reduced from mag. × 300.



A study of all marrow biopsies revealed that the fibrosis was often quite patchy and that intervening areas of hyperplastic myelopoiesis were common (Table 3).

CIRCULATING MEGAKARYOCYTE FRAGMENTS AND TISSUE MEGAKARYOCYTOSIS

The finding of megakaryocytes or nuclear fragments of these cells in the peripheral blood is common in myelofibrosis. Meticulous differential leucocyte counts were made on the 23 cases at the time myelofibrosis was diagnosed. Megakaryocyte fragments were seen in 15 of these patients (Fig. 2). Clumps of platelets with numerous atypical forms were common. Minot § described megakaryocyte fragments in chronic granulocytic leukemia, polycythemia, lobar pneumonia, Hodgkin's disease, and sepsis. In 1930 Downey [36] noted the numerous megakaryocytes in the spleen and liver of a case of atypical myelosis with circulating megakaryocytes. Megakaryocytes in the blood and tissue has been noted in case reports.|| It is believed that splenomegaly with myeloid metaplasia and increased megakaryocytes may be characteristic of myelosclerosis.[41] Whitby [42] has reemphasized that the presence of megakaryocytes in the blood of patients with leukemia or erythremia may indicate a change in the character of the disease. It is his feeling and ours that the finding of megakaryocyte fragments in the blood should suggest myelofibrosis. We have observed (Fig. 2) that megakaryocytosis may be a feature of a marrow biopsy associated with increased fibrosis and hyperplastic or hypoplastic cellularity.

GOUT AND HYPERURICEMIA

Hickling ¶ cites cases of nonleukemic myelosis with gouty arthritis and elevated blood uric acid. Hyperuricemia was noted in six of our patients (Table 4) and was not necessarily associated with the higher leucocyte levels. Gout has been associated with polycythemia.# The serum uric acid may rise to high levels,* and in one of our patients (Case 6) who had a serum uric acid of 18 mg/100 ml. there were no symptoms of gout. Case 9 developed typical gout while under observation for myelofibrosis, and there was a good response to colchicine therapy (Table 4).

RADIOCHROMATE AND RADIOIRON STUDIES IN MYELOFIBROSIS

The dynamics of erythropoiesis were studied in four patients (Cases 1, 2, 3, and 7) by use of radioiron and radiochromate. The erythrocyte survival studies are shown in Figure 6 and were all shorter than the normal range. Case 1 had a mildly shortened red cell survival. Her serum iron was 50γ and 35γ/100 ml. on two occasions. One-half of the injected radioiron was cleared from the plasma in 15 minutes, and there was 100% incorporation of the radioiron into the circulating erythrocytes in 15 days. In Case 2 the serum iron was 73γ/100 ml. and the time for clearance of one-half of the radioiron from the plasma was 25 minutes, and there was 65% incorporation of the iron in the erythrocytes in 14 days. Both of these patients excreted more than normal amounts of fecal urobilinogen (Table 4), and both patients have been able to maintain a normal hemoglobin level in spite of a shortened erythrocyte survival. An increased rate of plasma iron clearance is consistent with an increased rate of erythropoiesis. Case 3, who required frequent transfusions, showed a definitely shortened red cell survival by the radiochromate method, and his fecal urobilinogen was elevated. A radioiron study revealed the incorporation of only 12% of the isotope in 25 days. Case 7 was noted to have a spleen 7 cm. below the costal margin 22 years ago. Ten years ago he had a hemoglobin of 18 gm/100 ml. and a red blood cell count of 7,250,000/cu. mm. A lymph node and spleen biopsy at that time showed no specific

§ References 25 and 35.

|| References 12, 15, 18-20, 22, 30, 33, and 37-40.

¶ References 22 and 31.

References 19 and 43.

* References 39 and 44.

changes. Marrow aspiration revealed myeloid and erythroid hyperplasia with increased megakaryocytes. In 1950-1953 he received a total of 12 mc. of radiophosphorus, and later in 1954 he developed anemia. A sternal marrow aspiration in March, 1955, revealed a hyperplastic marrow, and a sternal biopsy showed extensive myelofibrosis (Fig. 3). The radiochromate cell survival was markedly shortened (Fig. 6), and he incorporated only 18% of the radioactive iron in his circulating erythrocytes in 15 days. There was an elevation of the fecal urobilinogen, and the guaiac tests on the stool were negative. Shortly thereafter the patient developed massive gastrointestinal bleeding and was

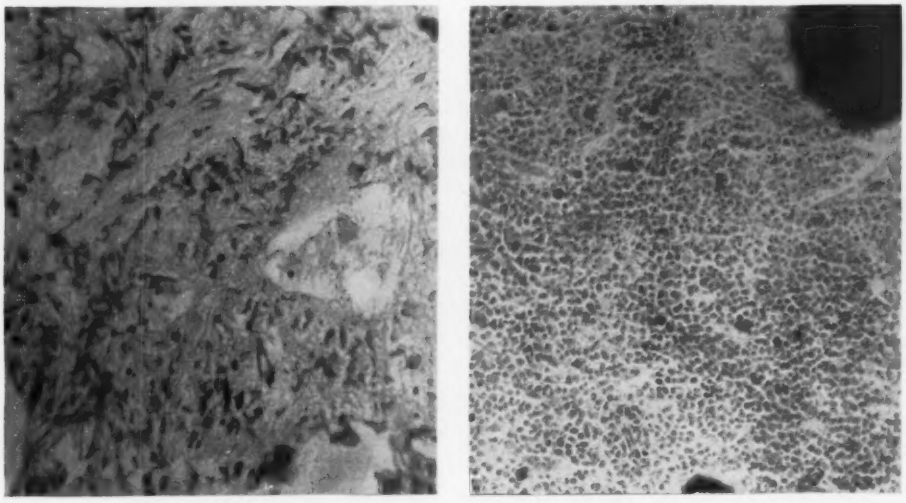
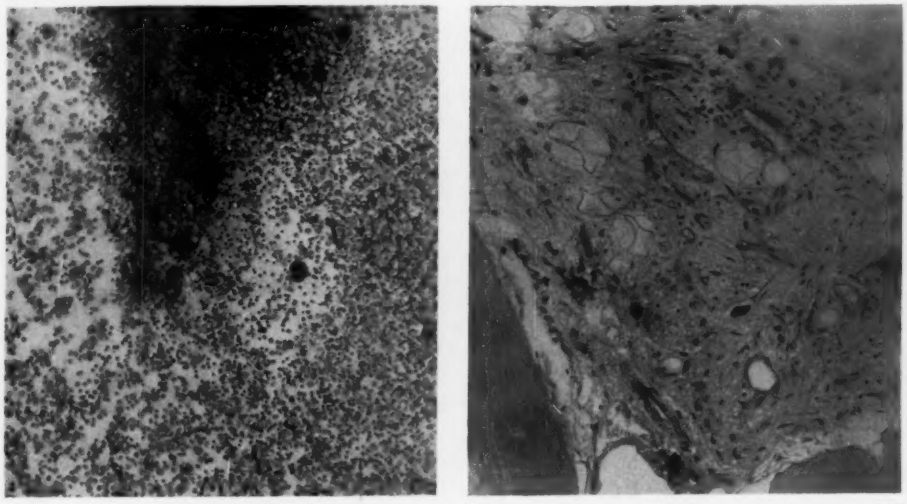


Fig. 3.—Evidence for the patchy nature of myelofibrosis. Above (Case 6): Left, sternal marrow biopsy specimen showing extensive myelofibrosis; reduced from mag. × 300. Right, postmortem section of vertebra one month after the sternal biopsy. Only myeloid hyperplasia was noted in the vertebra and the rib specimens; reduced from mag. × 150. Below (Case 7): Left, adequate sternal aspiration smear with 30% erythroid cells; reduced from mag. × 75. Right, sternal marrow biopsy specimen one week after the aspiration, showing myelofibrosis and little cellularity; reduced from mag. × 150.



found by x-ray to have a mass in the stomach. At operation a benign leiomyoma was excised from the stomach and the 500 gm. spleen was also removed. The response of the hemolytic anemia following splenectomy has been satisfactory, with a rise in hemoglobin to 11.6 gm/100 ml. and a fall in reticulocytes to 2.8%.

ERYTHROCYTE ABNORMALITY

A fairly marked variation in size and shape of the red cells has been noted and is depicted in Table 2. A poikilocytosis and anisocytosis was of marked degree in 18 patients at the time or stage of the disease when myelofibrosis was established. A fairly consistent red cell variant is a "teardrop" form [20] or elliptical form.[30] Teardrop forms were noted in 18 of these cases; some of these patients had normal hemoglobin levels. Nucleated red blood cells were noted in the peripheral blood in all but one case.

EXTRAMEDULLARY HEMOPOIESIS

The ectopic formation of blood is also referred to as myeloid metaplasia,[17] and it is seen maximally in the spleen. This is a common finding in myelofibrosis, but it may also be found in a variety of other conditions and prior to the development of myelofibrosis.† Originally, it was generally held that myeloid metaplasia represented a compensatory mechanism for degenerative changes in the marrow. Recent theories have considered the foci of myelopoiesis outside of the marrow as part of a general myeloproliferative disorder.‡ Extramedullary hemopoietic foci may be found in places other than the spleen, and in our cases the liver, lymph nodes, kidneys, and a subcutaneous nodule also demonstrated myeloid metaplasia. Of the 23 patients with myelofibrosis, 11 were shown to have myeloid metaplasia as established by biopsy or autopsy. The incidence might have been higher had spleen and liver biopsies been performed in the other 12 patients.

DIAGNOSIS

Evidence of osteosclerosis as a patchy increase in density of the marrow cavity with retained cortex has been described with myelofibrosis.§ These changes in the bone x-rays provided the first clue to the diagnosis in several of our patients. X-ray changes are not necessarily present when the biopsy shows myelofibrosis. Hickling [22] found that two of seven cases had x-ray evidence of osteosclerosis. Rosenthal and Erf [30] noted 6 of 17 patients with diagnostic x-ray changes. In this series (Table 3) 48% of the patients had x-ray changes suggestive of osteosclerosis. Of the positive roentgenograms all but two revealed changes in more than one bone. The femora were osteosclerotic in eight patients; ribs, in seven; pelvis, in five, and the spine, in four patients. It would seem that a bone survey by x-ray is of definite value in establishing a diagnosis; however, negative x-rays do not exclude myelofibrosis.

Diagnosis may be quite difficult because of the patchy nature of the fibrosis in the marrow. Opinion based on a single biopsy or aspiration without other substantiating evidence may be misleading.‖ Case 6 is of interest in that 10 years prior to study at this hospital she had been told that she had leukemia. A month before she died myelofibrosis was suspected and a sternal biopsy showed extensive fibrous change. At autopsy marrow specimens (Fig. 3) were taken from the rib and lumbar vertebrae, and these revealed a predominantly hyperplastic marrow, and the spleen, kidney, and liver showed myelopoietic centers.

TREATMENT

Roentgen therapy to the spleen in this disease has been regarded as ineffective or harmful.¶ Occasionally the patient may experience relief from discomfort due to an enlarged spleen.[20] Five of the patients here reported received x-ray therapy to the spleen

† References 45 and 46.

‡ References 45 and 47.

§ References 5, 8, 9, and 41.

‖ References 5, 15, 23, and 41.

¶ References 17 and 20.

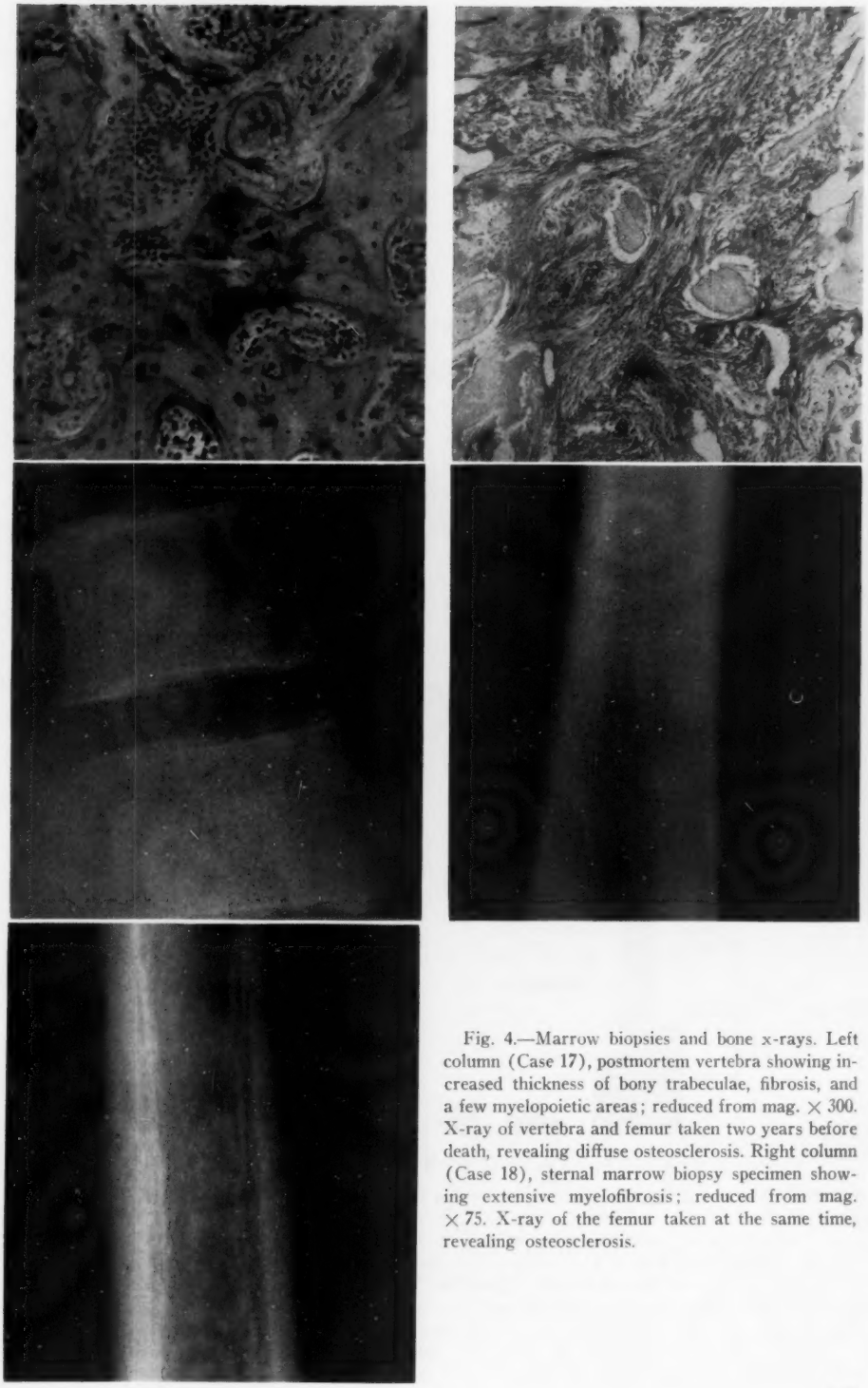


Fig. 4.—Marrow biopsies and bone x-rays. Left column (Case 17), postmortem vertebra showing increased thickness of bony trabeculae, fibrosis, and a few myelopoietic areas; reduced from mag. × 300. X-ray of vertebra and femur taken two years before death, revealing diffuse osteosclerosis. Right column (Case 18), sternal marrow biopsy specimen showing extensive myelofibrosis; reduced from mag. × 75. X-ray of the femur taken at the same time, revealing osteosclerosis.

with a fall in leucocyte level and some relief of symptoms, but there was no improvement of the anemia or apparent change in the course of the disease. Two patients (Cases 3 and 14) received a long course of Myleran (1,4-bis[methylsulfonyloxy]butane), without apparent benefit. Five of the patients (Cases 1, 2, 12, 15, and 19) had no therapy other than cortisone and transfusions.

HEMOLYTIC ANEMIA AND SPLENECTOMY

The subject of splenectomy in myeloid metaplasia has been reviewed by Hickling [22] and, more recently, by Green and co-workers.[21] Death shortly after splenectomy has been noted.# Recently there have been reports of benefit from splenectomy in

References 17 and 40.

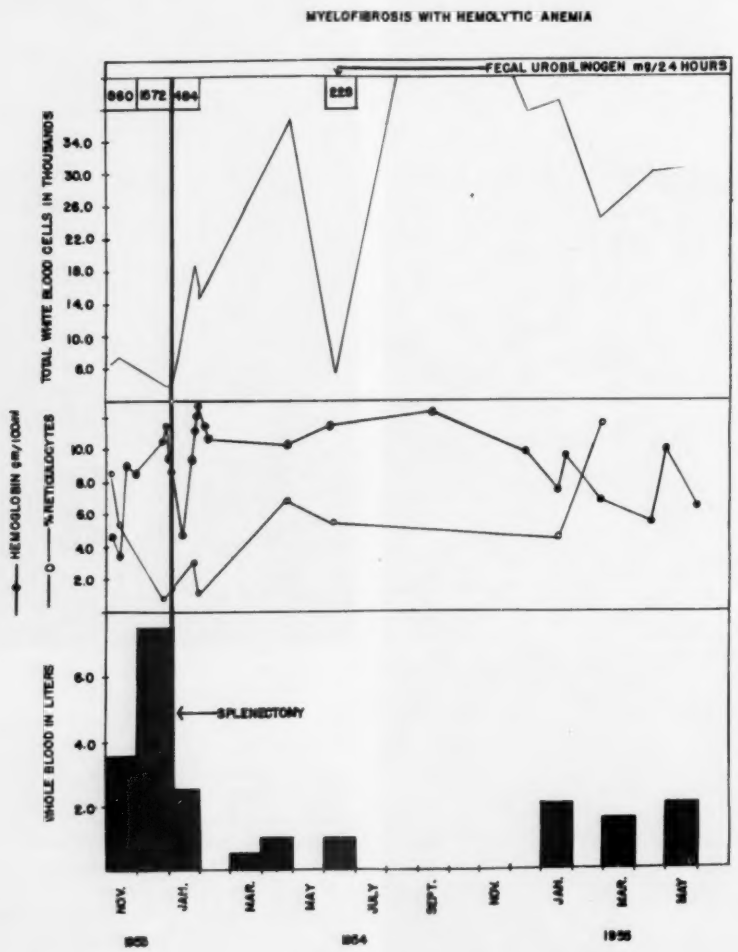


Fig. 5 (Case 4).—Graphic course of myelofibrosis with response following splenectomy, which was performed because of a severe hemolytic anemia. Jan. 4, 1954, marked by a dark vertical line, is the date of the splenectomy. The spleen weighed 2600 gm. and revealed foci of extramedullary hemopoiesis. The black bars at the bottom represent transfusions. On Sept. 13, 1954, the leucocyte level was 79,000, and the blood picture is that of leukemia at the present time. This patient was remarkably better for a year after splenectomy, but subsequently his need for transfusion has suggested anerythrogenesis.

those cases where a hemolytic anemia was present.* Case 4 (Fig. 5) was completely incapacitated and needed three or four transfusions a week. After splenectomy he improved and received only five transfusions during the next year, and there is some question as to whether or not these were necessary. In our present state of knowledge we consider severe hemolytic anemia as the only indication for splenectomy in patients who have myelofibrosis. A mild degree of reticulocytosis is surprisingly common, and the reticulocytes were more than 3% in 16 of our cases. This may be due to premature delivery of erythrocytes to the circulation by a small marrow mass operating under stress. Excessive hemolysis in patients with myelofibrosis and splenomegaly is also a likely cause of reticulocytosis. Fecal urobilinogen excretion (Table 4) was elevated in nine of the patients. From these data and the radiochromium studies of erythrocyte survival it appears that some increase in the rate of hemolysis is common in patients with myelofibrosis and splenomegaly.

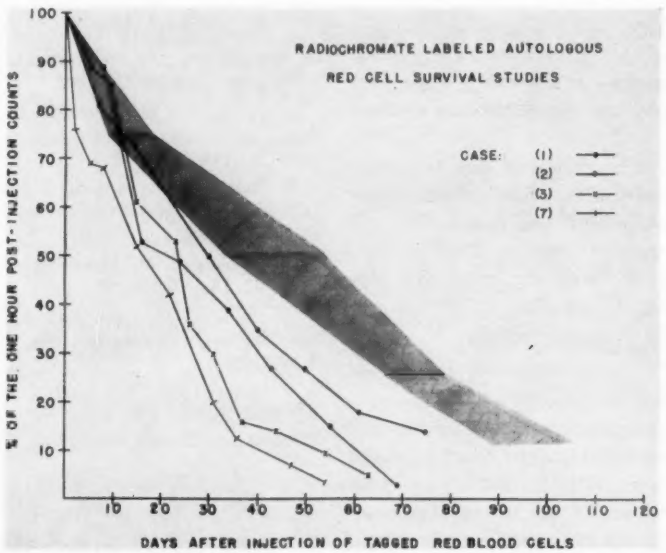


Fig. 6.—Cr^{51}-tagged red cell survival curves in four patients with myelofibrosis. The gray band represents the normal range for this laboratory. Autologous nonwashed red cells after one hour incubation with 100 μc of radiochromate were used in Cases 1, 2, and 3. Homologous nonwashed cells were used in Case 7. One hour postinjection specimens were used to represent 100% survival. These are apparent survival curves, as no correction for elution has been attempted.

SUMMARY

The following are concepts of myelofibrosis developed from a study of 23 patients and a perusal of some of the pertinent literature. None of the patients included in this report had metastatic carcinoma or tuberculosis. The existence of myelofibrosis was demonstrated by biopsy or autopsy study of bone marrow sections.

History.—The patient notes an insidious development of weakness, splenomegaly, weight loss, and anemia. Polycythemia, leukemoid blood picture, or gout may have been previously diagnosed. Splenomegaly may have been noted for months without other symptoms.

Physical Examination.—A prominently enlarged nontender spleen was observed in 19 out of 23 patients. Frequently gross splenomegaly was out of proportion to the apparent well-being of the patient. Hepato-

* References 10, 29, 48, and 49.

megaly was present in nearly every patient. Lymph node enlargement is not a feature of this syndrome.

Laboratory Data.—The hemoglobin level is most commonly low but may be normal or elevated. Normoblasts and teardrop-shaped erythrocytes were consistently observed in the peripheral blood. Wide variation in the total leucocyte count (2,000 to 200,000/cu. mm.) with a leukemoid neutrophilic distribution was the usual finding.

Circulating fragments of megakaryocytes were usually found, and their presence should arouse the suspicion of myelofibrosis. Unusual forms of platelets were commonly observed.

An elevated basal metabolic rate was found in all those patients in whom the determination was made, and hyperuricemia was not uncommon.

Evidence for an increased rate of hemolysis was obtained in some patients from the fecal urobilinogen and reticulocyte and erythrocyte survival studies. Two patients with prominent hemolytic processes have had a significant reduction in anemia and hemolysis following splenectomy.

Bone x-rays were interpreted as showing osteosclerosis in half of these patients.

Attempts to aspirate marrow from multiple sites usually resulted in dry taps or produced hypocellular (sinus) blood. Subsequent marrow biopsy revealed patchy myelofibrosis, increased thickness of bony trabeculae, hyperplastic foci of myelopoiesis, and often increased megakaryocytes. Simultaneous marrow biopsies in a single patient may differ markedly with respect to myelofibrosis and myeloid hyperplasia. Consecutive biopsies in various stages of the disease may show progression of myelofibrosis.

Prognosis and Other Observations.—Since several of the patients here reported died within two years of the onset of symptoms, the prognosis in this syndrome is not necessarily better than in typical chronic granulocytic leukemia.

Myelofibrosis may exist in any stage of chronic granulocytic leukemia and is not necessarily part of the terminal picture. It may exist prior to any therapy for leukemia.

Myelofibrosis may be found during the polycythemic as well as in the "spent" phase of polycythemia vera.

Miss Ethel Thewlis and Miss Frances K. Morris did the blood studies on all these patients; Dr. O. O. Meyer made clinical observations on many of these patients; Dr. L. W. Paul reviewed the x-rays and provided material on Case 17, and Dr. Walter Jaeschke made the interpretations of most of the biopsy material.

REFERENCES

1. Wood, H. C.: On the Relations of Leukocythaemia and Pseudoleukaemia, Am. J. M. Sc. **62**: 373, 1871.

2. Heuck, G.: Zwei Fälle von Leukämie mit eigenthümlichem Blut- resp. Knochenmarksbefund, Arch. path. Anat. **78**:475, 1879.

3. Sippy, B. W.: Splenic Pseudoleukaemia (Anaemia Splenica, Splenamegalie Primitive), Am. J. M. Sc. **118**:428, 1899.

4. Sippy, B. W.: A Critical Summary of the Literature in Splenic Pseudoleukemia, Am. J. M. Sc. **118**:570, 1899.

5. Chapman, E. M.: Osteosclerotic Anemia, Am. J. M. Sc. **185**:171, 1933.

6. Stephens, D. J., and Bredeck, J. F.: Aleukemic Myelosis with Osteosclerosis, Ann. Int. Med. **6**:1087, 1933.

7. Mettier, S. R., and Rusk, G. Y.: Fibrosis of the Bone Marrow (Myelofibrosis) Associated with a Leukemoid Blood Picture, Am. J. Path. **13**:377, 1937.

8. Vaughan, J. M.: Leuko-Erythroblastic Anemia, J. Path. & Bact. **42**:541, 1936.

9. Vaughan, J. M., and Harrison, C. V.: Leuco-Erythroblastic Anemia and Myelosclerosis, J. Path. & Bact. **48**:339, 1939.

10. Cartwright, G. E.; Finch, C. A.; Loeb, V.; Moore, C. V.; Singer, K., and Dameshek, W.: Panels in Therapy: II. Splenectomy in Myeloid Metaplasia with Myelosclerosis, Blood **10**:550, 1955.

11. Dameshek, W.: Some Speculations on the Myeloproliferative Syndrome, Editorial, Blood **6**: 372, 1951.

12. Block, M., and Jacobson, L. O.: Myeloid Metaplasia, J. A. M. A. **143**:1390, 1950.

13. Black-Schaffer, B., and Stoddard, L. D.: Panmyelosis and Chronic Granulocytic Leukemia, Am. J. Path. **29**:413, 1953.

14. Erf, L. A., and Herbut, P. A.: Primary and Secondary Myelofibrosis, Ann. Int. Med. **21**:863, 1944.

15. Heller, E. L.; Lewisohn, M. G., and Palin, W. E.: Aleukemic Myelosis, Am. J. Path. **23**:327, 1947.

16. Hewer, T. F.: Megakaryocytic Myelosis with Osteosclerosis, J. Path. & Bact. **45**:383, 1937.

17. Jackson, H.; Parker, F., and Lemon, H. M.: Agnogenic Myeloid Metaplasia of the Spleen, New England J. Med. **222**:985, 1940.

18. Jordon, H. E., and Scott, J. K.: A Case of Osteosclerosis with Extensive Extramedullary Hemopoiesis and a Leukemic Blood Reaction, Arch. Path. **32**:895, 1941.

19. Beattie, J. W., and Witney, J. L.: Polycythaemia, Leuco-Erythroblastosis, and Myelosclerosis, Brit. M. J. **2**:414, 1953.

20. Cook, J. E.; Franklin, J. W.; Hamilton, J. E., and Fowler, W. M.: Syndrome of Myelofibrosis, A. M. A. Arch. Int. Med. **91**:704, 1953.

21. Green, T. W.; Conley, C. L.; Ashburn, L. L., and Peters, H. R.: Splenectomy for Myeloid Metaplasia of the Spleen, New England J. Med. **248**: 211, 1953.

22. Hickling, R. A.: Chronic Non-Leukemic Myelosis, Quart. J. Med. **6**:253, 1937.

23. Paolino, W.: The Syndrome of the Pseudo-Leukemic (Pseudo-Erythremic) Myelosis, Acta haemat. **2**:86, 1949.

24. Wyatt, J. P., and Sommers, S. C.: Chronic Bone Marrow Failure, Myelosclerosis and Extramedullary Hematopoiesis, Blood **5**:329, 1950.

25. Minot, G. R., and Buckman, T. E.: Erythremia, Am. J. M. Sc. **166**:469, 1923.

26. Dameshek, W.: Physiopathology and Course of Polycythemia Vera as Related to Therapy, J. A. M. A. **142**:790, 1950.

27. Rosenthal, N., and Bassen, F. A.: Course of Polycythemia, Arch. Int. Med. **62**:903, 1938.

28. Wasserman, L. R.: Polycythemia Vera—Its Course and Treatment: Relation to Myeloid Metaplasia and Leukemia, Bull. New York Acad. Med. **30**:343, 1954.

29. Dameshek, W.: Some Observations in Polycythemia Vera, Bull. New England Med. Center **16**:53, 1954.

30. Rosenthal, W., and Erf, L. A.: Clinical Observations on Osteopetrosis and Myelofibrosis, Arch. Int. Med. **71**:793, 1943.

31. Hickling, R. A.: Gout, Leukemia and Polycythemia, Lancet **1**:57, 1953.

32. Churg, J., and Wachstein, M.: Osteosclerosis, Myelofibrosis, and Leukemia, Am. J. M. Sc. **207**: 141, 1944.

33. Schwartz, E.: Extramedullary Megakaryocytosis in Chronic Myelosis, Am. J. Clin. Path. **24**: 629, 1954.

34. Long, R. S.; Simmons, E. E., and Schenken, J. R.: Myeloid Metaplasia with Terminal Leukemia, J. A. M. A. **152**:1619, 1953.

35. Minot, G. R.: Megacaryocytes in the Peripheral Circulation, J. Exper. Med. **36**:1, 1922.

36. Downey, H.; Palmer, M., and Powell, L.: The Origin of the Megakaryocytes in the Spleen and Liver in a Case of Atypical Myelosis, Folia haemat. **41**:55, 1930.

37. Carpenter, G., and Flory, C. M.: Chronic Nonleukemic Myelosis, Arch. Int. Med. **67**:489, 1941.

38. Downey, H., and Nordland, M.: Hematologic and Histologic Study of a Case of Myeloid Megakaryocytic Hepato-Splenomegaly, Folia haemat. **62**: 1, 1939.

39. Peace, R. J.: Myelonecrosis, Extramedullary Myelopoiesis and Leukoerythroblastosis: A Mesenchymal Reaction to Injury, Am. J. Path. **24**:1029, 1953.

40. Reich, C., and Rumsey, W.: Agnogenic Myeloid Metaplasia of the Spleen, J. A. M. A. **118**: 1200, 1942.

41. Hynes, M.: Aleukaemic Leukaemia, Quart. J. Med. **9**:177, 1940.

42. Whitby, L. E. H.: The Significance of Megakaryocytes in the Periferal Circulation, Blood **3**: 934, 1948.

43. Moschcowitz, E.: Biology of Disease, New York, Grune & Stratton, Inc., 1948.

44. Merskey, C.: Chronic Nonleukemic Myelosis, Arch. Int. Med. **84**:277, 1949.

45. Rosenthal, M. C.: Extramedullary Hemopoiesis: Myeloid Metaplasia, Bull. New England M. Center **12**:151, 1952.

46. Taylor, H. E., and Simpson, W. W.: Bone Marrow Fibrosis Developing in Aleukemic Myelosis, Blood **5**:348, 1950.

47. Hutt, M. S. R.; Pinniger, J. L., and Wetherby-Mein, G.: The Myeloproliferative Disorders with Special Reference to Myelofibrosis, Blood **8**: 295, 1953.

48. Franks, R. B.: Myelofibrosis, Proc. Roy. Soc. Med. **45**:30, 1952.

49. Loeb, V.; Moore, C. V., and Dubach, R.: The Physiologic Evaluation and Management of Chronic Bone Marrow Failure, Am. J. Med. **15**:499, 1953.

Venous Thrombosis and Obscure Visceral Carcinoma

Report of Ten Cases

SAMUEL PERLOW, M.D.
and
JORDAN L. DANIELS, M.D., Chicago

The frequent occurrence of venous thrombosis in cases of malignancy either as a postoperative complication or in the terminal stages is general knowledge. But the association of superficial and deep vein thrombosis with obscure and often asymptomatic carcinoma is not so well known. This was first noted by Trousseau * in 1865 and again by Osler [1] in 1900, and over the years an occasional case report of this association has appeared in the medical literature.

That there is some increase in the thrombosing tendency of the blood in cases of malignancy is evident from all statistical reports, both operative and postmortem. What the relationship is has not been adequately determined as yet. In 1938, in a review of 125 instances of carcinoma of the body and tail of the pancreas discovered at postmortem examination Sproul [2] found an associated distant venous thrombosis in 56.2% as compared with only 9.7% when the carcinoma was found in the head of the pancreas or in other viscera. In 1943 Kenney [3] reported similar findings.

These reports suggested that there was some factor in pancreatic activity which had an effect upon venous thrombosis. The recent investigations by Innerfield † indicate that there is a relationship between the level of trypsin in the blood and the antithrombin titer. He believes that in acute pancreatitis the hemorrhagic tendency is due to hypertrypsinemia and the associated elevated antithrombin level and that in carcinomatous destruction of the body and tail of the pancreas there is a tendency toward venous thrombosis which is due to lowering of the trypsin level in the blood and an associated drop in the antithrombin level. This interesting work has not been entirely corroborated.[9] Even if true, this theory could not explain the occurrence of venous thrombosis in cases of carcinoma elsewhere. Recurrent venous thrombosis has been reported in cases with obscure carcinoma later located in the pancreas,‡ lung,§ gall bladder,|| uterus,[12] ovary,[16] and stomach.¶ In most of the case reports the episodes of thrombosis had been present for some time before the carcinoma was discovered and the lesion was inoperable when discovered. Nevertheless, the prognosis is not entirely a hopeless one, as is illustrated in a patient with bronchogenic carcinoma reported by Fisher [11] and in another with carcinoma of an ovary reported by Womack and Castellano [16] in whom the lesion was operable. In each instance the episodes of migrating phlebitis ceased after removal of the primary lesion.

Clinically the attacks of venous thrombosis may antedate the symptoms of the visceral carcinoma by weeks or months, especially

Submitted for publication Oct. 3, 1955.

From the Department of Surgery, Michael Reese Hospital, and the Chicago Medical School.

* Trousseau, A., cited by Sproul.[2]

† References 4 and 5.

‡ References 6-9.

§ References 10 and 11.

|| References 13 and 14.

¶ References 13 and 14.

if the latter is located in a silent organ such as the pancreas or the periphery of the lung. The thrombophlebitis is usually mild in character and is frequently migrating, and it may involve either the superficial or the deep veins in an extremity, neck, chest, abdominal walls, and pelvis. Pulmonary embolism is rare but may occur. Anticoagulant therapy does not seem to prevent the spread or migration of the venous thrombosis or the pulmonary embolism, which may occur even during treatment.

Microscopically the lesion appears as a low-grade inflammatory process involving the media and the adventitia with minimal fibroblastic changes in the thrombus. In some cases the thrombus is of the bland variety, without inflammatory changes in the vein wall. No malignant cells are seen.

REPORT OF CASES

CASE 1.—A 54-year-old white male physician was first examined on June 26, 1951, for superficial venous thrombosis of three weeks' duration and varicose veins in both lower extremities. Bilateral saphenous vein ligation was performed two weeks later. In August, 1951, he developed areas of superficial thrombophlebitis in both arms. He had no other complaints. Results of complete examination at that time, including laboratory studies, were entirely normal except for a rapid sedimentation rate. In September, 1951, abdominal exploration revealed a carcinoma of the tail of the pancreas with liver metastases. He developed postoperative iliofemoral vein thrombosis which subsided on bed rest. He died four months later.

Comment.—The initial attack of venous thrombosis seemed to be the usual type commonly associated with varicose veins in a man who seemed well otherwise. An obscure neoplasm was suspected after the appearance of areas of venous thrombosis in the arms but could not be demonstrated until exploratory laparotomy revealed a far-advanced carcinoma of the tail of the pancreas.

CASE 2.—A 44-year-old white man was examined July 16, 1951, because of an area of acute superficial venous thrombosis in the left leg of one week's duration. He also complained of occasional left chest pain and a slight dry cough of three months' duration. A chest roentgenogram revealed a small amount of fluid in the left pleural cavity which upon examination was found to contain carcinoma cells. The primary lesion was found in the left lower lobe bronchus. Typical migratory superficial phlebitis developed in the right leg five months later, three days before he died.

Comment.—Symptoms due to the carcinoma of the lung were present three months before the onset of thrombophlebitis, but it was the latter condition which brought the patient for medical consultation. The primary lesion was already far-advanced and inoperable when discovered.

CASE 3.—A 67-year-old white woman entered Michael Reese Hospital Feb. 10, 1952, because of superficial thrombophlebitis of the right thigh of three weeks' duration. During the preceding four months she had lost 25 lb. Complete examination revealed a continuous low fever and a left renal mass. Gastrointestinal roentgenograms and other laboratory examinations were negative. The mass proved to be a simple renal cyst at surgical exploration. The postoperative period was complicated by bilateral migrating superficial venous thrombosis. Despite adequate bishydroxycoumarin (Dicoumarol) therapy bilateral femoral vein thrombosis also developed. This patient died of pneumonia and a cerebral vascular accident two months after the first sign of venous thrombosis appeared. Postmortem examination revealed carcinoma simplex in the tail of the pancreas, with widespread metastases to the liver.

Comment.—A malignancy was suspected in this patient from the onset. The only definite lesion found early on examination proved to be a benign renal cyst. Later carcinoma of the pancreas and the liver was suspected.

CASE 4.—A 32-year-old white woman entered the Mount Sinai Hospital May 17, 1952, with a 24-hour history of pain, progressive swelling, and slight cyanosis of the left lower extremity, including the lower one-third of the thigh. A diagnosis of progressive femoral vein thrombosis was made. The patient had an additional history of pain in the distribution area of the left sciatic nerve, weakness, and slight weight loss for three months previously. The femoral vein was ligated. During the convalescence a thorough medical, roentgen, and laboratory examination was made. The findings were entirely negative and failed to reveal the cause of the pain, weakness, or weight loss. Four months later she was readmitted to the hospital with a mass in the left lower abdomen. Exploration revealed a posterior abdominal wall abscess in the region of the sciatic nerve roots but not involving the blood vessels. The abscess was drained. A biopsy of the mass revealed an epidermoid carcinoma. The patient died one year later. Necropsy revealed generalized carcinomatosis. The primary tumor arose from parovarian tissue rests.

Comment.—An obscure carcinoma was suspected in this young woman after the unexplained onset of deep vein thrombosis. The unusual location and origin of the carcinoma made the diagnosis difficult. From the history it seems that the neoplasm had been present for at least three months before the onset of venous thrombosis.

CASE 5.—A 47-year-old white man was admitted to Michael Reese Hospital on March 20, 1953, with a painful swelling in the right side of the neck. The right external jugular vein was found to be thrombosed, and there were several enlarged cervical lymph nodes in the posterior triangle. One week later he developed right subclavian and axillary vein thrombosis associated with marked edema of the entire right upper extremity. Despite anticoagulent therapy an area of superficial thrombophlebitis developed in the left leg. A chest roentgenogram revealed a tumor shadow in the right upper lobe. Sputum studies were positive for malignant cells. Biopsy of a cervical lymph node revealed metastatic squamous-cell carcinoma. Several weeks later he developed a dry cough. Prior to his death, two months after the first appearance of thrombophlebitis, this patient developed right femoral vein thrombosis.

Comment.—In this patient the pulmonary lesion was small, but it had already metastasized, as evidenced by the cervical lymph node involvement at the time of the venous thrombosis. He had no symptoms referable to the chest until several weeks after the appearance of migrating thrombophlebitis. The antithrombin titer in this patient was below normal.

CASE 6.—A 47-year-old white man was admitted to Grant Hospital on July 21, 1953, with a history of having had an attack of superficial thrombophlebitis involving the right leg five weeks previously. This was followed by similar involvement of the right thigh two weeks later. A dry cough had been present since three weeks before the onset of the phlebitis. Roentgen examination of the chest revealed changes suggesting pneumonitis or pulmonary infarction. When the chest findings failed to clear after adequate treatment, bronchoscopic examination was performed and revealed a bronchogenic carcinoma of the left main bronchus. It was found to be inoperable, upon thoracotomy. The patient died three months later.

Comment.—The cough, which was undoubtedly due to the carcinoma of the lung, was mild throughout the illness and seemed to be overshadowed by the symptoms of the phlebitis which brought the patient to the physician.

CASE 7.—A 65-year-old white woman was admitted to the Lutheran Deaconess Hospital Sept. 19, 1953, because of superficial thrombophlebitis of the left lower extremity of two weeks' duration. She had previously been feeling well and had had no complaints. Shortly after her hospitalization the deep veins of the left lower extremity became involved, and she suffered a pulmonary embolus two days later. In spite of anticoagulents the iliofemoral thrombosis progressed, the extremity became massive and cyanotic (phlegmasia cerulea dolens), and gangrene of the foot supervened. She died 12 hours after amputation of the extremity. Postmortem examination revealed bronchopneumonia, left iliac vein thrombosis, and carcinoma of the cecum.

Comment.—A far-advanced carcinoma of the cecum was present without symptoms. The venous thrombosis developed in the late stages of the malignancy and resulted in a pulmonary embolus and phlegmasia cerulea dolens with gangrene of the foot. It is interesting to note that the patient had several tarry stools shortly after starting anticoagulant therapy.

CASE 8.—A 43-year-old white man was in apparent good health until six weeks before his hospital admission, when he developed superficial thrombophlebitis in the right leg and, two weeks later, a similar involvement in the left leg. About the same time he developed a paroxysimal cough, for which he was admitted to Michael Reese Hospital on Oct. 31, 1953. A chest roentgenogram revealed a mass in the right upper lobe. Bronchoscopy and examination of bronchial smears confirmed the diagnosis of carcinoma. Subsequently there was extension of the superficial thrombophlebitis to the deep veins bilaterally. The patient refused a thoracotomy. He died suddenly in another hospital three weeks later of a massive pulmonary embolus.

Comment.—The venous thrombosis seemed to develop before the onset of the pulmonary symptoms, but from the roentgen examination the carcinoma of the lung was already fairly well advanced. Whether this lesion was resectable could not determined. The antithrombin titer was normal.

CASE 9.—A 60-year-old white woman entered the South Chicago Community Hospital on April 29, 1954, because of migrating thrombophlebitis involving both lower extremities of three weeks' duration. At the onset only the superficial veins were in-

volved, but later the deep veins became affected. She had lost between 20 and 30 lb. during the previous year, which she attributed to a reducing regimen. She had no gastrointestinal complaints. There was a moderate anemia and leucocytosis. Gastrointestinal roentgenographic examination revealed a fungating lesion in the distal half of the stomach. Surgical exploration of the abdomen revealed a carcinoma of the stomach with extensive metastases. She died on the 10th postoperative day.

Comment.—Although there were no symptoms referable to the gastrointestinal tract, the weight loss and slight anemia associated with migrating phlebitis aroused suspicion of an underlying carcinoma. A far-advanced gastric carcinoma was found.

CASE 10.—A 62-year-old white woman was admitted to the Woodlawn Hospital on Sept. 5, 1954, because of edema of the right forearm of four weeks' duration and recent weight loss. Nine years previously she had had a bilateral oophorectomy and hysterectomy for carcinoma of the ovaries. Four months before the present hospital admission she had had superficial thrombophlebitis in the right thigh. On examination there was a moderate anemia; the chest was clear, and no abdominal mass or liver enlargement was palpable. There was slight edema of the right forearm and evidence of healed superficial thrombophlebitis in the right thigh. Two days after admission she developed edema of the left leg, and several days later the right leg became edematous. Both extremities became markedly edematous and cyanotic to the groins over the next two days, and gangrene of the whole left foot and the right big toe developed (phlegmasia cerulea dolens). She died of a pulmonary embolus on Sept. 14, 1954. Postmortem examination revealed metastatic ovarian carcinoma in the lung, the liver, and the retroperitoneal region. Both femoral and iliac veins and the vena cava to the level of the renal veins were thrombosed. The pulmonary arteries were occluded by nonadherent thrombi.

Comment.—The recurrent venous thrombosis and the history of carcinoma of the ovaries nine years previously suggested metastatic carcinoma to the clinician in spite of the absence of corroborative findings. This patient had both superficial and deep vein thrombosis, and terminally the picture was that of bilateral phlegmasia cerulea dolens with gangrene of the feet. It is interesting to note that for about eight and one-half years she had no symptoms referable to metastatic carcinoma. It would seem that the carcinoma must be well advanced before venous thrombosis occurs. This assumption is borne out by the fact that in this series and in most of the reported cases the carcinoma was beyond the stage of operability when venous thrombosis developed.

COMMENT

We have summarized the protocols of 10 patients who presented themselves with migrating venous thrombosis and in whom obscure carcinoma was discovered. There were two cases of carcinoma of the body and tail of the pancreas, four cases of carcinoma of the lung, one case of carcinoma of the cecum, one case of carcinoma of parovarian rest tissue, one case of carcinoma of the ovary, and one case of carcinoma of the stomach. The duration of the episodes of venous thrombosis from their onset to the discovery of an asymptomatic carcinoma, or until symptoms developed which were attributed to a carcinoma in retrospect, varied between two weeks and four months. In seven of our cases the malignant lesion was inoperable when the vein thrombosis occurred. In two cases (Cases 4 and 8) it was impossible to determine whether the carcinoma was or was not operable at that time, and in one case (Case 7) the carcinoma of the cecum was operable as determined at postmortem examination when the patient died after a thigh amputaion.

Obscure carcinoma should be considered in cases of recurrent migrating thrombophlebitis which cannot be attributed to any of the known associated causes as operations, pregnancy, blood dyscrasias, thromboangiitis obliterans, prolonged bed rest, etc. A thorough search should be made of the various organs, with use of all available diagnostic methods. Although in most of the reports of carcinoma so discovered the lesion was inoperable, in a few an operable neoplasm was found. It is possible that greater awareness on the part of the physician of the possible association of venous thrombosis and carcinoma may result in earlier diagnosis and increase the number of operable cases.

It is interesting to note that anticoagulant therapy did not prevent progression of the

Summary of Ten Cases of Thrombosis with Obscure Carcinoma

Hospital Admission Date	Age, Yr.	Sex	Type of Vein Involvement: Superficial	Type of Vein Involvement: Deep	Type of Vein Involvement: Embolism	Duration of Thrombosis Before: Diagnosis of Malignancy	Duration of Thrombosis Before: Primary Carcinoma	Diagnosis Made by
1. 6/20/51	54	M	+	+	..	3 mo.	Tail of pancreas	Surgery
2. 7/16/51	44	M	+	..	..	2 wk.	Lung	Pleural fluid
3. 3/10/52	67	F	+	+	..	2 mo.	Body & tail of pancreas	Autopsy
4. 5/12/54	32	F	..	+	..	4 mo.	Parovarian tissue rest	Surgery
5. 3/20/53	47	M	+	+	..	2 wk.	Lung	Bronchoscopy
6. 7/21/53	47	M	+	+	..	2 mo.	Lung	Surgery
7. 9/19/53	65	F	+	+	+	1 mo.	Cecum	Autopsy
8. 10/31/53	43	M	+	+	+	6 wk.	Lung	Bronchoscopy
9. 4/29/54	60	F	+	+	..	3 wk.	Stomach	Surgery
10. 9/ 5/54	62	F	+	+	+	4 mo.	Ovarian metastases	Autopsy

venous thrombosis or involvement of new areas or pulmonary embolism in these cases. We have observed on a number of occasions # that a gastrointestinal carcinoma will bleed, sometimes profusely, when the patient is receiving anticoagulants. In Case 7 of this report, with carcinoma of the cecum, tarry stools were noted after the institution of anticoagulant therapy. It seems to us that administration of an anticoagulant and examination of the stool for blood may often aid in the diagnosis of gastrointestinal carcinoma.

REFERENCES

1. Osler, W., and McCrae, T.: Latent Carcinoma of the Stomach, Philadelphia M. J. **5**:245, 1900.

2. Sproul, E. E.: Carcinoma and Venous Thrombosis: The Frequency of Association of Carcinoma in the Body or Tail of the Pancreas with Multiple Venous Thrombosis, Am. J. Cancer **34**:566, 1938.

3. Kenney, W. E.: Association of Carcinoma in the Body and Tail of the Pancreas with Multiple Venous Thrombi, Surgery **14**:600, 1943.

4. Innerfield, I.; Angrist, A., and Benjamin, J. W.: Plasma Antithrombin Patterns in Disturbances of the Pancreas, Gastroenterology **19**: 843, 1951.

5. Innerfield, I.; Angrist, A., and Benjamin, J. W.: Antithrombin Titer in Acute Pancreatitis, Am. J. Med. **12**:24, 1952.

6. Jennings, W. K., and Russell, W. O.: Phlebothrombosis Associated with Mucin-Producing Carcinomas of the Body and Tail of the Pancreas, Arch. Surg. **56**:186, 1948.

7. Gore, I.: Thrombosis and Pancreatic Carcinoma, Am. J. Path. **29**:1093, 1953.

8. Storer, J., and Kasdan, P.: The Relation of the Pancreas to Blood Coagulation, Surgery **33**: 683, 1953.

9. McLachlin, J.; Paul, R., and Paterson, J. C.: A Critical Evaluation of the Antithrombin Test for Venous Thrombosis, Surg. Gynec. & Obst. **94**:297, 1952.

10. Gross, F. O.; Jaehning, D. B., and Coker, W. G.: Association of Migratory Thrombophlebitis with Carcinoma, North Carolina M. J. **12**:97, 1951.

11. Fisher, M. M.; Hochberg, L. A., and Wilensky, N. D.: Recurrent Thrombophlebitis in Obscure Malignant Tumors of the Lung: Report of 4 Cases, J. A. M. A. **147**:1213, 1951.

12. Pratt, G. H.: Surgical Significance and Management of Pathologic Blood Clotting, Surg. Gynec. & Obst. **97**:589, 1953.

13. Edwards, E. A.: Migrating Thromphlebitis Associated with Carcinoma, New England J. Med. **240**:26, 1949.

14. Lipman, M. D., and Taber, J. N.: Peripheral Manifestations of Visceral Carcinoma, Gastroenterology **16**:188, 1950.

15. Cooper, T., and Barker, N. W.: Recurrent Venous Thrombosis: An Early Complication of Obscure Visceral Carcinoma, Minnesota Med. **27**: 31, 1944.

16. Womack, W. S., and Castellano, C. J.: Migratory Thrombophlebitis Associated with Ovarian Carcinoma, Am. J. Obst. & Gynec. **63**:467, 1952.

Unpublished data.

A Comparative Study of the Treatment of Essential Hypertension

The Effect of Rauwolfia and a Rauwolfia Compound (Rauwolfia, Mannitol Hexanitrate, and Rutin)

SYDNEY STONEHILL, M.D., Rochester, N. Y.

Although Rauwolfia has been used in India for centuries because of its sedative effect in such conditions as insanity, hysteria, insomnia, etc., it was not until 1933 that its hypotensive effect was reported.[1] In 1931 Siddiqui and Siddiqui [2] were able to isolate five crystalline alkaloids from the whole alkaloid Reserpine. These compounds have been used in combination with other hypotensive drugs such as hexamethonium, pentolinium (pentapyrrolidinium), hydralazine, and Veratrum alkaloids.* This study concerns itself with the hypotensive effect of the powdered whole root from Rauwolfia micrantha alone and when combined with rutin and mannitol hexanitrate (Maxitate).

MATERIALS AND METHODS

A total of 17 patients with moderate to severe hypertension were observed for a period of one year. The blind test technique was used. All tablets were of identical appearance, and were labeled 7-71, 7-72, and 7-73. The composition of the tablets is as follows:

7-71	Rauwolfia micrantha.....	30 mg.
7-72	Placebo	.....
7-73	Rauwolfia micrantha.....	30 mg.
	Rutin	30 mg.
	Mannitol hexanitrate.....	30 mg.

Submitted for publication Aug. 17, 1955.

Department of Internal Medicine, Rochester General Hospital.

This study was made possible through a grant-in-aid from R. J. Strasenburgh Co., Rochester, N. Y.

* References 3-8.

The contents of the tablets were unknown to the investigator throughout the study. The dosage was two tablets four times daily. The first patient studied was started on 7-71, the second on 7-72, the third on 7-73, and the fourth on 7-71, etc. At the end of six months those patients receiving 7-71 were given 7-72, and those on 7-73 were given 7-71, without their being aware of the change.

Prior to starting, a chest x-ray, electrocardiogram, urinalysis, complete blood cell count, NPN determination, and urea-clearance test was done on each patient, and preliminary blood pressures were determined. The chest x-ray, electrocardiogram, and urea-clearance test were repeated at six-month intervals, while the urinalysis, complete blood cell count, and NPN determination were repeated every three months. All patients were ambulatory and were seen every two weeks, at which time blood pressures were taken in both arms in the sitting and lying positions. The heart rate and size were ascertained. Funduscopic examinations were made every month. At every visit each patient was questioned as to symptoms relating to the central nervous, cardiovascular, gastrointestinal, and genitourinary systems. In all, there were 12 patients who received 7-71, 11 patients who received 7-72, and 11 patients who received 7-73 for a six-month period.

The clinical diagnosis of each of the patients included in this study is as follows:

Patient	Diagnosis
F. F.	Arteriosclerotic heart diesase, pulmonary edema
C. K.	Essential hypertension, coronary artery disease
C. D.	Essential hypertension
L. R.	Essential hypertension
A. L.	Arteriosclerotic heart disease, pulmonary edema
A. S.	Essential hypertension, hypertensive encephalopathy
A. W.	Angina pectoris

TABLE 1.—*Average Blood Pressures of All Seventeen Patients*

Case	Age, Yr.	Sex	Av. Blood Pressure, Mm. Hg															
			Prior to Treatment				Rauwolfia				Placebo				Mannitol Hexanitrate with Rauwolfia Compound			
			SRA*	LRA*	SLA*	LLA*	SRA	LRA	SLA	LLA	SRA	LRA	SLA	LLA	SRA	LRA	SLA	LLA
F. F.	63	F	182/102	182/102	182/102	182/102	183/84	172/74	180/86	172/81	183/86	171/79	179/85	174/83	.....	.....	.....	.....
C. K.	45	M	230/90	276/94	294/90	284/94	227/68	229/77	236/64	236/79	.....	.....	.....	.....	246/70	246/79	253/67	255/80
C. D.	55	M	180/110	180/110	180/110	180/110	159/88	159/84	169/89	167/89	172/84	165/88	179/99	180/98	.....	.....	.....	.....
L. R.	43	M	210/130	180/110	210/120	210/120	214/117	196/101	213/116	213/116	205/117	191/108	204/116	206/117	.....	.....	.....	.....
A. L.	70	F	208/88	200/80	200/96	206/86	.....	.....	.....	.....	229/91	222/93	237/98	225/95	235/87	224/86	239/90	238/90
A. S.	35	F	200/110	200/110	200/110	200/110	.....	.....	.....	.....	193/110	185/103	190/110	185/107	165/96	163/93	165/97	166/96
A. W.	76	F	174/86	178/86	192/92	182/78	166/76	172/74	181/85	184/80	.....	.....	.....	.....	167/78	184/78	186/85	183/84
V. M.	34	F	220/120	220/120	220/120	220/120	.....	.....	.....	.....	219/142	214/128	220/133	219/132	219/132	207/127	214/130	211/127
H. S.	74	M	254/94	240/90	254/96	240/90	233/89	218/80	234/88	222/85	236/94	228/88	236/88	234/89	.....	.....	.....	.....
M. F.	47	F	178/88	200/100	184/94	200/96	.....	.....	.....	.....	177/85	179/86	177/87	182/89	149/73	150/71	148/75	158/76
L. S.	60	F	180/90	170/86	180/88	176/88	216/99	207/95	214/96	213/96	.....	.....	.....	.....	201/93	196/89	202/92	196/88
F. C.	53	F	180/94	180/94	180/94	176/90	145/77	143/73	147/81	146/78	.....	.....	.....	.....	160/82	158/79	160/84	165/84
C. T.	70	F	232/100	222/100	242/100	228/102	200/78	194/74	209/78	204/77	.....	.....	.....	.....	199/84	198/86	215/88	210/90
M. C.	81	F	200/88	208/84	174/80	192/84	210/91	207/87	214/94	210/90	210/96	214/92	216/100	216/95	.....	.....	.....	.....
A. .N	54	F	218/120	214/106	218/120	210/110	223/129	221/126	222/126	225/129	.....	.....	.....	.....	225/129	229/127	229/131	232/134
C. B.	54	F	260/120	250/110	264/122	246/110	229/108	222/105	224/108	223/106	229/120	222/108	233/120	223/113	.....	.....	.....	.....
C. H.	46	F	230/132	218/130	236/134	220/130	.....	.....	.....	.....	232/128	224/127	223/130	223/127	184/111	189/108	186/111	188/109

* SRA, sitting, right arm; LRA, lying, right arm; SLA, sitting, left arm; LLA, lying, left arm.

TABLE 2.—*Average Change of Blood Pressure*

Case	Age, Yr.		Av. Change of Blood Pressure, Mm. Hg: Rauwolfia SRA*	Rauwolfia LRA*	Rauwolfia SLA*	Rauwolfia LLA*	Placebo SRA	Placebo LRA	Placebo SLA	Placebo LLA	Mannitol Hexanitrate with Rauwolfia Compound SRA	Mannitol Hexanitrate with Rauwolfia Compound LRA	Mannitol Hexanitrate with Rauwolfia Compound SLA	Mannitol Hexanitrate with Rauwolfia Compound LLA
F. F.	63	S*	+ 1	10	2	10	+ 1	11	3	8	....	....	....	....
		D*	18	28	17	21	16	23	17	19	....	....	....	....
C. K.	45	S	3	47	58	48	....	....	....	....	+14	30	41	29
		D	22	17	26	15	....	....	....	....	20	15	23	14
C. D.	55	S	21	21	12	13	8	15	1	0	....	....	....	....
		D	22	26	21	21	16	22	11	12	....	....	....	....
L. R.	43	S	+ 4	+16	+ 3	+ 3	5	+11	6	4	....	....	....	....
		D	3	9	4	4	3	2	4	3	....	....	....	....
A. L.	70	S	....	....	....	....	+13	+ 6	+21	+ 9	+19	+ 8	+31	+22
		D	....	....	....	....	10	8	4	6	15	16	12	18
A. S.	35	S	....	....	....	....	7	15	10	15	35	37	35	34
		D	....	....	....	....	0	7	0	3	14	17	13	14
A. W.	76	S	6	6	11	+ 2	....	....	....	....	7	2	6	+ 1
		D	10	12	7	+ 2	....	....	....	....	8	7	7	+ 6
V. M.	34	S	....	....	....	....	1	6	0	1	1	13	6	9
		D	....	....	....	....	+22	+ 8	+13	+12	+12	+ 8	+10	+ 7
H. S.	74	S	21	22	20	18	18	12	18	6	....	....	....	....
		D	5	16	8	5	0	2	8	1	....	....	....	....
M. F.	47	S	....	....	....	....	+ 1	23	7	18	29	50	36	42
		D	....	....	....	....	2	15	7	7	15	28	20	20
L. S.	60	S	+28	+19	+26	+25	....	....	....	....	+13	+ 8	+14	+ 8
		D	+ 3	1	0	0	....	....	....	....	3	7	4	8
F. C.	53	S	35	37	33	30	....	....	....	....	16	22	20	11
		D	17	21	13	12	....	....	....	....	8	14	10	8
C. T.	70	S	32	28	33	24	....	....	....	....	33	24	27	18
		D	22	25	22	25	....	....	....	....	16	14	12	12
M. C.	81	S	+10	1	+40	+18	+10	+ 6	+42	+24	....	....	....	....
		D	+ 3	+ 3	+14	+ 6	+ 8	+ 8	+20	+11	....	....	....	....
A. M.	54	S	+ 5	+ 7	+ 4	+15	....	....	....	....	+ 7	+15	+11	+22
		D	+ 9	+20	+ 6	+19	....	....	....	....	+ 9	+21	+11	+24
C. B.	54	S	31	28	41	23	31	28	31	23	....	....	....	....
		D	12	5	14	4	0	2	2	+ 3	....	....	....	....
C. N.	46	S	....	....	....	....	+ 2	+ 6	13	+ 3	46	29	50	32
		D	....	....	....	....	4	3	4	3	21	22	23	21

* S, systolic pressure; D, diastolic pressure; SRA, sitting, right arm; LRA, lying, right arm; SLA, sitting, left arm; LLA, lying, left arm.

V. M. Essential hypertension, coronary artery disease

H. S. Essential hypertension, generalized arteriosclerosis

M. F. Essential hypertension, left hemiplegia

L. S. Arteriosclerotic heart disease, angina pectoris, cardiac failure

F. C. Essential hypertension

C. T. Arteriosclerotic heart disease, right hemiplegia

M. C. Arteriosclerotic heart disease, cardiac failure

A. M. Arteriosclerotic heart disease, coronary artery disease

C. B. Essential hypertension

C. H. Essential hypertension, angina pectoris

RESULTS

Table 1 depicts average blood pressures of all 17 patients during the period of treatment. All patients had had known hypertension for at least two years prior to onset of therapy. Three patients (F. F., A. L., and A. S.) had had one or more bouts of pulmonary edema; two patients (M. F. and C. T.) had suffered a hemiplegia; one patient (A. S.) had an episode of acute hypertensive encephalopathy; one patient (C. K.) had aortic insufficiency and chronic cardiac failure, and two patients (A. W. and C. H.) had severe angina. Of those patients who had pulmonary edema, only one (F. F.) had several more episodes of acute edema during the first three months of therapy, and she has had none since. The two patients with angina had less pain and accordingly used less glyceryl trinitrate (nitroglycerin).

Table 2 shows the average change of blood pressure in each patient while under therapy. Patient C. K. had the greatest systolic fall (58 mm. Hg), while patient M. F. had the greatest fall of diastolic pressure (28 mm. Hg).

Table 3 presents the average lowering of blood pressure in all 17 patients. These figures include those who have had an actual rise in blood pressure while under therapy.

TABLE 3.—*Average Lowering of Blood Pressure of All Seventeen Patients*

		Av. Lowering of Blood Pressure, Mm. Hg			
		SRA*	LRA*	SLA*	LLA*
Rauwolfia (12 patients)	S*	8.6	13.2	11.4	8.6
	D*	9.7	10.9	9.3	6.5
Placebo (11 patients)	S	5.0	7.4	2.4	3.5
	D	1.9	6.2	2.2	2.5
Mannitol hexanitrate with Rauwolfia compound (11 patients)	S	10.4	16.0	15.0	11.1
	D	9.0	10.0	9.4	6.6

* S, systolic; D, diastolic; SRA, sitting, right arm; LRA, lying, right arm; SLA, sitting, left arm; LLA, lying, left arm.

Table 4, however, depicts the average lowering of blood pressure only in those patients who have shown a fall of pressure. It can readily be seen that those patients who have obtained an actual fall in blood pressure comprise at least two-thirds of the series. The fall is greatest with Rauwolfia plus rutin and mannitol hexanitrate, less with Rauwolfia alone, and least with the placebo. It was noticed that the failures occurred in the patients with severe hypertension of long standing.

TABLE 4.—*Average Lowering of Blood Pressure Only of Those Patients Who Have Shown a Fall of Blood Pressure*

		Av. Lowering of Blood Pressure, Mm. Hg			
		SRA*	LRA*	SLA*	LLA*
Rauwolfia (12 patients)	S*	20.3 (7)†	20.0 (10)	26.3 (8)	23.7 (7)
	D*	14.6 (9)	15.4 (10)	13.2 (10)	11.9 (9)
Placebo (11 patients)	S	11.6 (7)	15.7 (7)	9.9 (9)	9.4 (8)
	D	5.7 (9)	9.3 (9)	6.3 (9)	8.0 (8)
Mannitol hexanitrate with Rauwolfia compound (11 patients)	S	23.9 (7)	25.9 (8)	27.6 (8)	25.0 (7)
	D	13.3 (9)	15.5 (9)	13.8 (9)	13.8 (8)

* S, systolic pressure; D, diastolic pressure; SRA, sitting, right arm; LRA, lying, right arm; SLA, sitting, left arm; LLA, lying, left arm.
† The number of patients is given in parentheses.

All patients, including those taking the placebo, were more relaxed. However, the greatest sense of well-being occurred in those who were taking Rauwolfia. There was a noticeable lowering of pulse rate in all patients, but it was least marked in those taking the placebo. No reactions were noted in any patients other than a rather persistent complaint of tiredness when taking Rauwolfia. The results of the chest x-rays, electrocardiograms, blood chemistry studies, blood cell counts, and urinalyses were essentially unchanged. It should be emphasized that there was no progressive deterioration in the clinical status of any patient. One woman (A. W.) developed pernicious anemia which responded to vitamin B_{12}.

COMMENT

An attempt has been made to compare the clinical and hypotensive effect of Rauwolfia micrantha alone and mannitol hexanitrate with Rauwolfia compound. The patients took both of the above drugs, or an identical-appearing placebo, over a six-month period of time, at the end of which, unknown to the patient, a change was made. It was felt that a six-month period on one drug was adequate to assess the patient's reaction to the medication and also to give the investigator an opportunity to make comparative observations. As mentioned above, reports have appeared in the literature pertaining to the hypotensive effect of Rauwolfia alone or in combination with such drugs as hexamethonium, pentolinium, hydralazine, and Veratrum alkaloids. No studies have been reported on the clinical effect of Rauwolfia micrantha combined with rutin and mannitol hexanitrate.

Table 4 is illuminating in that it enables us to make the following observations:

1. Mannitol hexanitrate with Rauwolfia compound has a greater hypotensive effect than Rauwolfia alone.

2. The placebo can also reduce blood pressure, but not to the extent of the specific drugs. This, I believe, emphasizes the well-known psychosomatic effect of the doctor-patient relationship.

3. More than two-thirds of the patients treated with Rauwolfia or mannitol hexanitrate with Rauwolfia compound had an

adequate clinical response. No serious toxic effects were noted. While taking Rauwolfia the patients felt calm and free of anxiety. Many complained again of nervousness when, unknown to them, the placebo was substituted. For this reason, it is felt that Rauwolfia should not be denied those hypertensive patients who do not get an actual fall of their blood pressure. Failure to secure a hypotensive effect was observed in those patients whose hypertension was severe and of long standing and who suffered advanced arteriosclerosis.

SUMMARY AND CONCLUSION

The clinical effects of Rauwolfia micrantha, mannitol hexanitrate (Maxitate) with Rauwolfia compound, and a placebo were studied for a period of one year. Each patient was kept on one of these drugs for six months before starting another for the next six months. The blind test technique was used, with tablets of identical appearance whose content was unknown to the observer. The results indicate that an adequate hypotensive response was obtained with Rauwolfia. This effect was enhanced when mannitol hexanitrate with Rauwolfia compound was used.

REFERENCES

1. Chopra, R. N.; Gupta, J. C., and Mukherjee, B.: The Pharmacological Action of an Alkaloid Obtained from Rauwolfia Serpentina Benth, Indian J. M. Res. **21**:261, 1933.

2. Siddiqui, S., and Siddiqui, R. N.: Chemical Examination of the Roots of Rauwolfia Serpentina Benth, J. Indian Chem. Soc. **8**:667, 1931.

3. Wilkins, R. W.: New Drug Therapies in Arterial Hypertension, Ann. Int. Med. **37**:1144, 1952.

4. Wilkins, R. W., and Judson, W. E.: The Use of Rauwolfia Serpentina in Hypertensive Patients, New England J. Med. **248**:48, 1953.

5. Ford, R. V., and Moyer, J. H.: Preliminary Observations of Rauwiloid Hexamethonium Combined Therapy of Hypertension, Am. Heart J. **46**: 754, 1953.

6. Smirk, F. H.; Doyle, A. E., and McQueen, E. G.: Control of Blood Pressure by Combined Action of Reserpine and Pentapyrrolidinium, Lancet **2**:159, 1954.

7. Naegele, C. F.; Rosenman, R. H.; Hoffman, C. L., and Friedman, M.: Combined Rauwolfia-Hydralazine Therapy of Hypertensive Patients, Circulation **11**:182, 1955.

8. Doyle, A. E.; McQueen, E. G., and Smirk, F. H.: Treatment of Hypertension with Reserpine, with Reserpine in Combination with Pentapyrrolidinium, and with Reserpine in Combination with Veratrum Alkaloids, Circulation **11**:1402, 1955.

Suppression of Gastric Hydrochloric Acid Secretion by Enzyme Inhibitors

A New Approach in Research on the Therapy of Peptic Ulcer

FRANKLIN HOLLANDER, Ph.D.
and
HENRY D. JANOWITZ, M.D., New York

According to our current ideas concerning the pathogenesis of peptic ulceration, this disease is essentially a matter of localized autodigestion of the wall of the digestive tract by active gastric juice. This process does not occur unless there is a breakdown of some kind in the normal defensive mechanism of the gastrointestinal mucosa, the two-component mucous barrier.[1] Since we do not yet know how to strengthen or repair this defensive structure directly, all the medications in general use today for the therapy of this disease are designed to reduce the intensity of the aggressive agent, acid-pepsin juice—directly, by way of the enzyme, and indirectly, by reducing the intragastric acidity, upon which peptic action is dependent. Many of the pharmacological agents which reduce gastric acidity also, in some measure, relieve muscle spasm which makes for prolonged retention of stomach contents. Hence, a review of all chemotherapeutic agents presently in use resolves itself into a study of pharmacological devices for reducing gastric acidity. Since it is the purpose of this communication to discuss a new kind of acidity-reducing agent, it will be profitable to start by classifying those already available to us.

TABLE 1.—*Antacids*

Soluble alkalis
Sodium bicarbonate
Nonabsorbable alkalis
Magnesium oxide
Magnesium trisilicate
Calcium carbonate
Colloidal aluminum hydroxide
Aluminum phosphate gel
Exchange resins
Polyamine-methylene resin (Resinat)

All such chemical substances fall into either of two broad categories: (1) those which neutralize HCl already secreted into the gastric lumen and (2) those which block the stimuli which activate the acid-forming cells of the stomach. In the first group we find numerous alkalis, both soluble and insoluble, and ion-exchange resins, as indicated in Table 1. In the second group there are a host of substances, chiefly recent creations of the organic chemist, which block the action of acetylcholine, the neurohumoral agent released by vagal activity.* A list of the better-known drugs in this second category is pre-

Submitted for publication Aug. 12, 1955.

Gastroenterology Research Laboratory, The Mount Sinai Hospital.

Much of the experimental work discussed in this paper was carried out with the aid of grants from the Altman Foundation.

Read before the Section on Pathology and Physiology at the 104th Annual Meeting of the American Medical Association, Atlantic City, June 7, 1955.

* It is generally accepted that acetylcholine is liberated at the neuroglandular junction on arrival of a postganglionic impulse and that this substance is the agent which acts directly on receptor sites in the parietal cell wall. However, evidence is gradually accumulating from the work in our laboratory and elsewhere that histamine may be the final common chemical pathway, regardless of mode of stimulation, and that it is the agent which operates on these receptor sites. Arguments pro and con on this matter will be published elsewhere.

TABLE 2.—*Neural Blocking Agents*

Inhibitors of postganglionic cholinergic nerves
Belladonna tincture
Atropine
Homatropine methylbromide (Novatrin)
Methscopolamine bromide (Pamine)
Methantheline (Banthine)
Propantheline (Pro-Banthine)
Oxyphenonium (Antrenyl)
Penthienate (Monodral)
Diphemanil (Prantal)
Mepiperphenidol (Darstine)
Dibutoline (Dibuline)
Inhibitors of ganglia
Tetraethylammonium (TEA)
Hexamethonium bromide (C6)
Methscopolamine bromide (Pamine)
Methantheline (Banthine)
Propantheline (Pro-Banthine)
Oxyphenonium (Antrenyl)
Penthienate (Monodral)
Diphemanil (Prantal)
Mepiperphenidol (Darstine)

sented in Table 2. Thus, in general, the two types of medication in widespread use either reduce the intensity of stimuli acting upon the cell or simply reduce the concentration of acid already secreted. A different and even more direct approach in the search for an ideal therapeutic agent would be to attack the machinery of the acid-producing cell itself. How can this be done?

Following communication between any stimulus and the parietal cell, an extensive series of chemical reactions is set up which results ultimately in the formation of a solution of virtually pure HCl.† In the course of this train of reactions, many enzymes play a crucial role. Hence, if even one of these enzymatic processes could be blocked by inhibition of the enzyme which catalyzes it we would have available an agent for completely preventing the formation of HCl intracellularly, regardless of the intensity of stimulation. It is such compounds, capable of acting as enzyme inhibitors in vitro, which

† This HCl secretion appears to be free of all other anions and cations (i. e., Na^+, K^+, Ca^{++}, $H_2PO_4^-$, etc.) and nearly isosmotic with the tissue fluid from which it was derived. For a review of evidence on this point, see Reference 2.

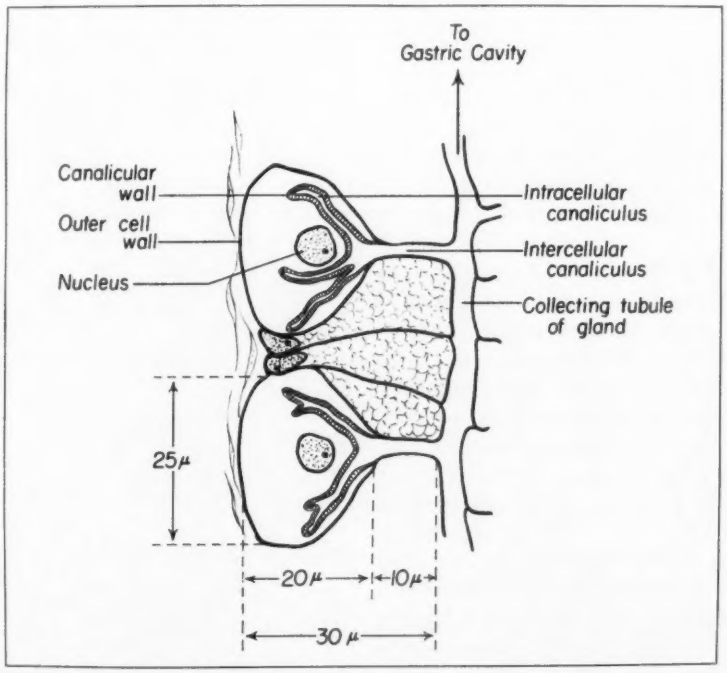


Fig. 1.—Diagrammatic representation of parietal cell (dimensions approximate).

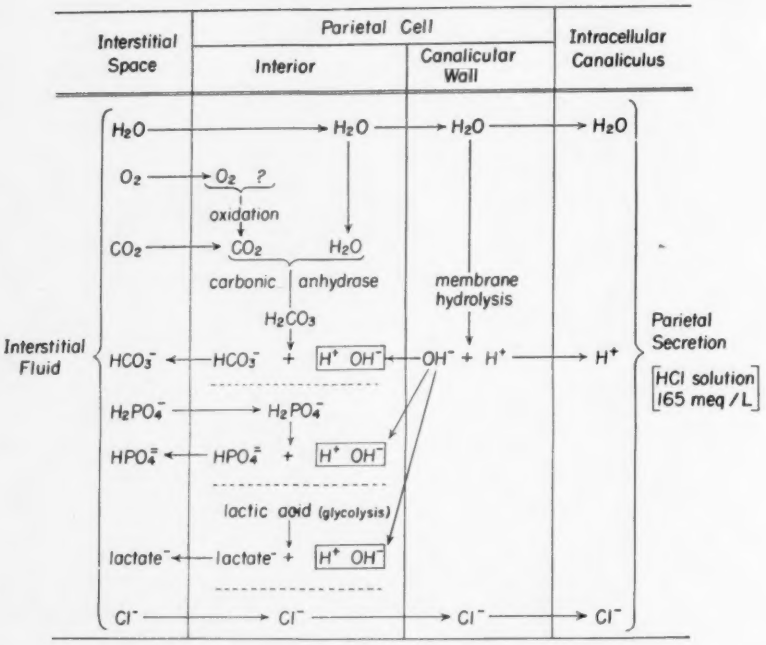


Fig. 2.—Chemistry of HCl formation by the parietal cell.

promise to give us this third category of agents for ulcer therapy. The present communication proposes to discuss some of the enzyme inhibitors which physiologists have already found effective disrupters of the acid-producing machinery of the parietal cells.

It is known today that the parietal cell contains a tubular arborization (Fig. 1), designated the "intracellular canaliculus," which empties through an intercellular canal into the lumen of the gastric gland and so into the gastric cavity proper. About 25 years ago, one of us [3] advanced the hypothesis that the actual site of formation of the HCl is in or on the boundary wall of this intracellular canaliculus and that this is the place where hydrolysis of neutral chlorides occurs, with simultaneous and instantaneous neutralization of the liberated hydroxide. Since then, this hypothesis has been amplified in many respects, and our present conception of this process is fairly well represented by the diagram in Figure 2.‡ It is noteworthy that the canalicular wall has recently [6] been found to be striated and to have considerable thickness, perhaps as great as 1μ in some cases, which lends further support to our early idea that this structure contains an important part of the acid-producing machinery. As a consequence of this, and also of the fact that osmotic forces tend to move water outward into the canaliculus, the parietal cell is capable of producing a strong acid without its ever coming in contact with the cytoplasm and so destroying the latter.

In order to understand the pertinent aspects of the cellular machinery, let us consider the diagram in Figure 3. The parietal cell is here divided into three major compartments: (1) the interior, which includes cytoplasm, nucleus, etc.; (2) the wall of the intracellular canaliculus, where the HCl is synthesized and ejected into the gastric cavity through the canaliculus itself, and (3) the cell wall proper, which contains the receptor sites for stimulation of secretion and also the membrane pores through which various substances (water, ions, nutrient

‡ References 4 and 5.

materials, and waste products) move into or out of the cell. Fluid, and its divers attendant solutes, moves from extreme left in the diagram to extreme right—from the blood stream to the gastric cavity. In the middle compartment, the cell interior, we conceive of three groups of reactions, each of which is dependent on enzyme catalysis in some measure: (*a*) those concerned with the basal metabolic activities of the parietal cell, (*b*) those concerned with the production of energy and possibly some particular chemical agents required for the synthesis and extrusion of the HCl secretion, and (*c*) the formation of H_2CO_3 by hydration of CO_2 which is derived in part from the gastric blood supply and in part from the forementioned metabolic activities. In the compartment at the right, the canalicular wall, there probably occurs one or more reactions required for the separation and transport of H ions or Cl ions, or both. Whether these reactions involve enzymatic processes is not yet evident, but it seems probable that such is the case here also. The movement of water is generally believed to occur "passively" and in response only to osmotic influences. Finally, in the compartment on the left, we find the membrane through which electrolytes, various anabolic and catabolic substances, and water move in either direction; there are also the receptor sites at which and through which stimulatory impulses are imparted to the cell to initiate or maintain its specialized activity, the generation and ejection of HCl solution. According to current patterns of thought, receptor site activity definitely involves enzymatic processes, and some schools believe that this is true for cell wall penetration also. Thus it may be that all six of these groups of chemicophysiological processes involve enzymes in some degree. In only one, however, has the nature of this enzyme been completely established—the hydration of CO_2 to H_2CO_3, which is speeded up greatly by the enzyme carbonic anhydrase.

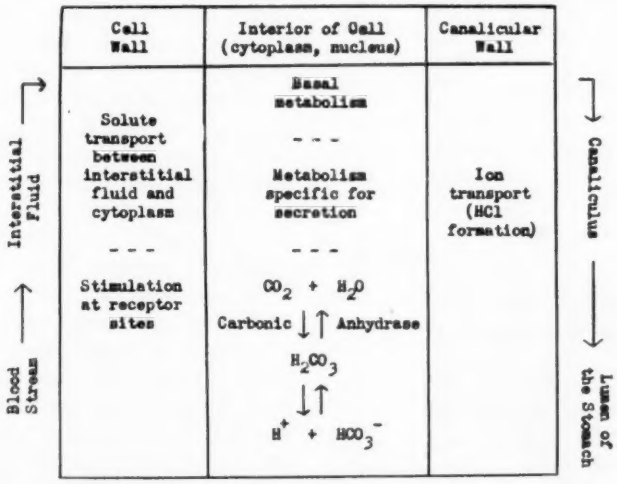


Fig. 3.—Classification of enzyme-catalyzed reactions according to location and function on the parietal cell.

And now, let us return to the problem of a new kind of ulcer therapy. It has been known for a long time that every enzymatic process can be blocked by means of one or more chemical substances, either through competition with the substrate for a position on the enzyme molecule or in some other way. Such enzyme inhibitors are generally specific for a single enzyme or for a group of structurally related enzymes. It is only natural, therefore, that physiologists should

try to take advantage of this phenomenon in an effort to disrupt (reversibly) the machinery of the parietal cell. As a result of research by numerous workers, we already have a considerable list of enzyme inhibitors (Table 3) which are known to be effective in blocking acid formation without destroying the tissue. Previous investigators of this phenomenon have worked with isolated preparations of mouse or frog stomach and with acute cat preparations; our own contributions have all been based on dogs provided with stomach pouches or on human subjects. Reference to Table 3 reveals that none of the inhibitors so far studied in this way operate against enzymes presumed to function in the wall of the intracellular canaliculus or in the outer wall of the cell proper. The majority of them are concerned with the metabolic reactions, and the rest, with the action of carbonic anhydrase.

TABLE 3.—*Enzyme Inhibitors Which Have Been Found to Block HCl Secretion*

	Experimental Animal	Reference No.
Basal and secretory metabolic processes in the cell interior		
$HgCl_2$	Cat	9
Iodoacetamide	Mouse	10
	Dog	11
n-ethylmaleimide	Mouse	10
	Dog	11
p-chloromercuribenzoate	Mouse	12
Fluoride	Frog	13
	Rat	14
	Cat	15
Fluoroacetate	Mouse	16
2,4-dinitrophenol	Mouse	16
	Dog	17
2,4-dinitro-6-phenylphenol	Dog	17
Azide	Frog	18
Cyanide	Rat	14
	Frog	18
Iodoacetate	Rat	14
	Frog	18
Arsenite	Rat	19
Tetramethyl-*p*-phenylenediamine	Rat	19
Formation of H_2CO_3 to neutralize OH ions (carbonic anhydrase)		
Acetazoleamide	Dog	7
	Man	8
2-benzenesulfonamide	Dog	17
2-benzenesulfonamido-1,3,4-thiadiazole-5-sulfonamide	Dog	17
Carzenide (Dirnate)	Dog	17
Sulfanilamide	Mouse	20
Thiophene-2-sulfanilamide	Mouse	20
p-toluenesulfonamide	Frog	21
p-sulfonamidebenzoate	Frog	21
Azosulfamide (Prontosil) soluble	Frog	21
Reactions concerned with H ion (and Cl ion?) transport in the canalicular wall		
None	.....	..
Reactions concerned with cell stimulation at receptor sites or with movement of solutes between intestinal fluid and cytoplasm		
None	.....	..

Unfortunately for our present purpose, the various basic metabolic reactions of the parietal cell appear to be essentially of the same character as those in tissue cells generally, i. e., reactions of the Krebs cycle, those involved in the coupling of oxidative processes and the production of high-energy phosphate bonds, etc. Hence, every enzyme inhibitor which has so far been found to block HCl production through these channels also interferes with other vital processes in the body and consequently is toxic systemically. Because of this, none of the inhibitors in this category has been studied in man, nor does it seem likely that the solution to our therapeutic problem is to be found here. These agents may also operate against metabolic processes which supply electrical or mechanical energy for the act of secretion, but as yet we have not been able to differentiate the two categories in any significant degree. When we have acquired insight into the latter group of reactions and know at least one of the enzymes operating in this latter way, it is reasonable to hope that some enzyme inhibitor may be found which is capable of blocking only the production of energy for the secretion proper and which will not interfere with the chemistry of other tissues. Even more promising than this is the search for enzymatic processes which are specific to HCl production but which operate in or on the canalicular wall.

Only in one of the six categories of reactions formulated in Figure 3 have significant results already been obtained. This category includes this single reaction sequence:

$$CO_2 + H_2O \rightleftarrows H_2CO_3 \rightleftarrows H^+ + HCO_3^-$$

which is catalyzed by the enzyme carbonic anhydrase. We have discussed elsewhere [5]

the cumulative experience of various physiologists who have studied this reaction in the parietal cell and looked for a suitable inhibitor of carbonic anhydrase which is likewise capable of blocking the production of HCl. In the course of this search, a number of compounds were shown by other investigators to be effective in some measure in vitro, in isolated gastric mucosal preparations (for references, see Table 3). The search finally culminated in the report from our laboratory that the compound acetazoleamide (2-acetylamino-1,3,4-thiadiazole-5-sulfonamide; Diamox) possesses this dual capability in vivo when administered to dogs with Heidenhain pouches, either intravenously or by topical application to the mucosa,[7] and that the acid production by histamine may be reduced by as much as 95% to 97%. Formation of the remaining 3% to 5% could not be prevented, because it arises from the uncatalyzed production of H_2CO_3 without the aid of the enzyme.

Since the toxicity of acetazoleamide is already known to be so low as to permit its use clinically as a diuretic agent, a similar investigation of its efficacy against gastric secretion in man was clearly indicated. The results of such a study in 25 patients either with ulcer disease or with some complaint not referable to the gastrointestinal tract indicate that the drug is as effective by the intravenous route in human subjects as in dogs and that it operates against histamine-induced secretions as well as against basal secretion.[8] The degree of inhibition did not become significant (i. e., over 50% of control values) until the dosage was raised above 61 mg. of acetazoleamide per kilogram of body weight. In general, a reduction of 90% or more was not effected until the dosage was raised above 95 mg/kg. In some instances, free HCl disappeared entirely; such 100% inhibition, however, is in contrast to a maximum of 95% to 97% in pouch dogs, and we believe that the difference is a result only of intragastric neutralization. It is interesting to note that the administration of acetazoleamide affects the quantity of HCl which is put out but does not influence the patterns of Na, K, or Cl concentrations and that the inhibitory effects are independent of alterations in plasma electrolytes. Also—and this is of the utmost importance for our clinical objectives—the inhibition of acid formation is completely reversible within 24 hours because, once the drug is excreted, the carbonic anhydrase resumes its function and HCl secretion reappears once more.

It might appear from these results that we have already attained the ideal medical therapy for peptic ulcer, but this is still far from being the case. The ideal therapeutic agent must effect more-or-less complete but reversible elimination of free HCl, at doses which are well below toxic limits, and the mode of administration must be oral. Acetazoleamide meets the first of these conditions amply and the second only moderately well, since no disturbing side-effects were elicited provided the dosage was kept below 100 mg/kg. It does not meet the third condition, however, since the oral dosage required to attain the same blood level of the drug as that which effects 95% inhibition by the intravenous route is so great as to be impractical. This last deficiency rules out acetazoleamide, but new carbonic anhydrase inhibitors are being synthesized today which possess physical and chemical characteristics differentiating them markedly from acetazoleamide itself, and it is our hope that some new compound of this kind may satisfy all of the specifications for the ideal ulcer therapy.

In the meanwhile, efforts to acquire insight into the fundamental chemical processes of the parietal cell continue, and we are still hopeful that one day substances will be found which operate specifically against the enzyme systems of the canalicular wall. Such substances, being specific in their action on the parietal cell, will not disturb enzymatic processes in other tissues of the body, and thus they may likewise satisfy the clinical requirements for the ideal ulcer therapy—perhaps even more efficiently than inhibitors of carbonic anhydrase action.

REFERENCES

1. Hollander, F.: The 2-Component Mucous Barrier: Its Activity in Protecting the Gastroduodenal Mucosa against Peptic Ulceration, A. M. A. Arch. Int. Med. **93**:107-120, 1954.

2. Hollander, F.: Gastric Secretion, Fed. Proc. **11**:706-714, 1952.

3. Hollander, F.: Theories of Hydrochloric Acid Formation in the Stomach, J. Am. Inst. Homœop. **22**:311-321, 1929.

4. Hollander, F.: The Composition and Mechanism of Formation of Gastric Acid Secretion, Science **110**:57-63, 1949.

5. Janowitz, H. D.; Colcher, H., and Hollander, F.: Carbonic Anhydrase Inhibition and Gastric Secretion, Tr. New York Acad. Sc. **15**:56-68, 1952.

6. Dalton, A. J.: Electron Microscopy of the Epithelial Cell Types of the Stomach and Intestine, J. Nat. Cancer Inst. **13**:983, 1953.

7. Janowitz, H. D.; Colcher, H., and Hollander, F.: Inhibition of Gastric Secretion of Acid in Dogs by the Carbonic Anhydrase Inhibitor, 2-Acetylamino - 1,3,4 - Thiadiazole - 5 - Sulfonamide, Am. J. Physiol. **171**:325-330, 1952.

8. Janowitz, H. D.; Dreiling, D. A., and Hollander, F.: Inhibition of Hydrochloric Acid Formation in the Human Stomach by Diamox: The Role of Carbonic Anhydrase in Gastric Secretion, read before the 47th Annual Meeting of the American Society for Clinical Investigation, Atlantic City, N. J., May 2, 1955.

9. Dreyer, N. B., and Leonard, C. S.: Effects of Mercury Salts on the Composition of the Gastric Juice, Arch. internat. pharmacodyne. **78**:86-92, 1949.

10. Davenport, H. W.: Inhibition of Gastric Acid Secretion by Iodoacetate Amide and N-Ethyl Maleimide, Am. J. Physiol. **179**:628, 1954.

11. Hollander, F.: Reversibility of the Inhibition of Gastric Acid Secretion by Iodoacetate Amide (IAA) and N-Ethyl Maleimide (NEM), Fed. Proc. **14**:75, 1955.

12. Davenport, H. W.: Inhibition of Gastric Acid Secretion by p-Chloromercuribenzoate, Fed. Proc. **13**:32, 1954.

13. Crane, E. E.; Davies, R. E., and Longmuir, N. M.: Relations between HCl Secretion and Electrical Phenomena in Frog Gastric Mucosa, Biochem. J. **40**:xxxvi, 1946.

14. Lutwak-Mann, C.: Metabolic Processes in the Gastric Mucosa, Biochem. J. **41**:19-29, 1947.

15. Bowie, J. Y.; Darlow, G., and Murray, M. M.: The Effect of Sodium Fluoride on Gastric Acid Secretion, J. Physiol. **122**:203-208, 1953.

16. Davenport, H. W., and Chavré, V. J.: Acid Secretion and Oxygen Consumption by Mouse Stomachs in Vitro, Am. J. Physiol. **174**:203-208, 1953.

17. Janowitz, H. D., and Hollander, F.: Varieties of Inhibition of HCl Secretion by Direct Application of Several Groups of Compounds to the Gastric Mucosa, Fed. Proc. **13**:247, 1954.

18. Davies, R. E.: The Mechanism of Hydrochloric Acid Production by the Stomach, Biol. Rev. **26**:87-120, 1951.

19. Patterson, W. B., and Stetten, D., Jr.: A Study of Gastric HCl Formation, Science **109**:256-258, 1949.

20. Davenport, H. W., and Jensen, V.: The Secretion of Acid by the Mouse Stomach in Vitro, Gastroenterology **11**:227-239, 1948.

21. Davies, R. E., and Edelman, J.: The Function of Carbonic Anhydrase in Gastric Mucosa, Biochem. J. **43**:lvii, 1948.

Acute Pancreatitis Complicating Diabetes Mellitus

ELAINE T. BOSSAK, M.D., New York
and
ROBERT H. JOELSON, M.D., Paterson, N. J.

The occurrence of permanent diabetes mellitus following attacks of acute and recurrent pancreatitis has been well established* Transient hyperglycemia and glycosuria have been noted frequently during acute attacks,[3] and in some instances patients with fulminating disease have died in diabetic coma.†

Scant attention has been devoted, however, to the converse development of acute pancreatitis in patients known to have preexisting diabetes mellitus. Recently, we observed the occurrence of acute pancreatitis in three hospitalized patients with previously known diabetes. This prompted a review of the hospital records from 1936 to 1954 of all patients in whom a final diagnosis of acute pancreatitis had been made on the basis of clinical and/or autopsy criteria. Excluded from consideration were children, cases following abdominal surgery, and instances of chronic pancreatitis. Among 103 hospitalized patients with acute pancreatitis, 5 additional instances of its association with preexisting diabetes mellitus were encountered.‡ Eight patients, therefore, are included as the subject matter of the present report.

Previous observers have reported a total of 31 patients in whom acute pancreatitis developed in the course of diabetes. Warren and LeCompte in a review of 811 autopsies performed on diabetic patients noted 12 cases of pancreatitis occurring 6 months to 13 years after onset of diabetes.[1] Four who had died in diabetic coma had been previously described by Root.[6] A review of 89 patients with pancreatitis by Rose yielded 7 instances in diabetics.[7] Bowers and Atkins reported 3 such cases among 17 autopsies performed on patients who died in diabetic coma.[8] An additional nine patients were added by other authors.§ Some patients included in a previous review have been omitted because clinical data were inadequate to characterize duration of diabetes in relation to the occurrence of pancreatitis.[8]

REPORT OF CASES

CASE 1.‖—In 1936, a 20-year-old white woman was discovered to have diabetes six months before admission and had received no therapy. She entered the hospital with severe upper abdominal pain of 24 hours' duration and had been comatose for 3 hours. On admission she was in deep coma, with Kussmaul respirations. Her temperature was 97.2 F; pulse rate, 140; respirations, 42, and blood pressure, 130/80. There was no abdominal tenderness. No reflexes were elicited. Lesions of xanthoma diabeticorum were noted on the dorsum of the hands. Urine examination revealed 4% sugar and 2+ acetone. White blood cell count was 6100/cu. mm., with 88% polymorphonuclear leucocytes. Fasting blood sugar was 450 mg. per 100 cc.; CO_2, 6 vol. %; serum cholesterol, 1250 mg. per

Submitted for publication Aug. 2, 1955.

From the Department of Medicine, The Mount Sinai Hospital, New York.

* References 1 and 2.

† References 4 and 5.

‡ Drs. A. Richman and D. Dreiling helped in the review of 52 of these cases.

§ References 3 and 9-14.

‖ This patient has been included in a previous report on pancreatitis by Beck.[15]

100 cc., and calcium, 10.8 mg. per 100 cc. The patient received 350 units of regular insulin over the following 12 hours and was given 2500 cc. of intravenous fluids. Her temperature rose to 105 F, and shock and anuria supervened two and one-half hours before death. At the time of death, 12 hours after admission, urine examination showed 2.5% sugar and a faint trace of acetone. Postmortem examination revealed the pancreas to be moderately firm, with fat necrosis of the surface and surrounding peritoneum. There was a small hemorrhage in the tail of the pancreas. Microscopic section showed extensive necrosis of the gland, with acute inflammatory reaction. The liver was moderately fatty. There was degeneration and swelling of the kidney tubules.

CASE 2.—A 62-year-old white woman was discovered to have diabetes 12 years before admission, in 1942, and was taking insulin. She had been hospitalized elsewhere, two and one-half months before admission, for a myocardial infarction and congestive heart failure with mild ketosis. She entered this hospital with severe epigastric pain, radiating to the back, of one day's duration, associated with dyspnea, vomiting, and a feeling of impending death. She appeared acutely ill, with Cheyne-Stokes respirations. Her blood pressure was 85/70. The liver was palpable 3 fingerbreadths below the costal margin. There was no abdominal tenderness. There were signs of mild congestive heart failure. Urine examination revealed moderate glycosuria. White blood count was 22,600, with polynucleosis and left shift. Blood sugar was 330 mg. per 100 cc.; CO_2, 59.6 vol. %, and urea nitrogen, 23 mg. per 100 cc. Electrocardiogram revealed evidence of an anterior wall myocardial infarct. The patient received small doses of regular insulin to control the glycosuria. She remained in shock, and the blood urea nitrogen rose to 107 mg. per 100 cc. before her death, on the sixth hospital day. Postmortem examination revealed the pancreas to be firm and slightly enlarged, with numerous areas of fat necrosis with severe destruction of the parenchyma and an acute inflammatory reaction. There was a healed myocardial infarct.

CASE 3.—A 49-year-old white woman was known to have had diabetes for eight years. She had been taking 40 units of protamine zinc insulin daily for only four months before admission, in 1945. Three weeks before admission she developed dull epigastric pain associated with anorexia and weight loss. Twelve hours before admission she began to vomit repeatedly and became very drowsy and almost unresponsive. On examination her temperature was 95.4 F and her blood pressure was 80/50. The skin and mucous membranes were dry, and the eyeballs were soft. There were no remarkable abdominal findings. Urine examination showed marked glycosuria and acetonuria. The white blood cell count was 28,000/cu. mm., with an increase in polymorphonuclear leucocytes. Blood sugar was 660 mg. per 100 cc., and CO_2 was 49.5 vol.%. During the first nine hours she received 1200 units of regular insulin and 3500 cc. of parenteral fluids, including 500 cc. of plasma. She remained stuporous. Blood pressure remained at shock levels until after transfusion of 500 cc. of whole blood, when it rose to 120/70. Acetonuria diminished, and after an additional 450 units of insulin it disappeared. At this time, 15 hours after admission, she was oriented but very restless. Shortly thereafter she showed signs of severe vascular collapse and died. Postmortem examination revealed a normal-sized orange-yellow pancreas. Microscopic examination showed focal interstitial pancreatitis and peripancreatitis, with localized abscess formation and thrombophlebitis.

CASE 4.—A 29-year-old white woman was a known diabetic who had required no insulin for five months before admission, in 1947. She had been on a drinking bout for several days and was brought to the hospital in stupor, with Kussmaul respirations and an acetone odor to her breath and markedly dehydrated. Blood pressure was 110/70. The abdomen was diffusely rigid. Urine on examination showed 4+ reactions for sugar, acetone, and diacetic acid. Blood sugar was 530 mg. per 100 cc., and CO_2 was 7.8 vol.%. During the first six hours she received 595 units of regular insulin and 4200 cc. of parenteral fluid, including 500 cc. of plasma. She excreted less than 100 cc. of urine during this time. Respiratory distress, cyanosis, and marked tachycardia supervened, and she died about 12 hours after admission. Postmortem examination showed acute fibrinopurulent inflammation of the pancreas, with foci of necrosis. The liver was fatty. The kidneys disclosed moderate degeneration of the proximal convoluted tubules. There was severe pulmonary edema.

CASE 5.—In 1948, a 46-year-old white woman had had diabetes for seven years and was maintained on 8 to 15 units of protamine zinc insulin daily. Three days before admission she had an episode of severe upper abdominal pain lasting six hours. One day before admission dull pain recurred, radiating to both shoulders and to the back. On the day of admission she began to vomit and experienced a shaking chill. On admission there was tenderness and rebound tenderness in the epigastrium and both upper abdominal quadrants. There was some left costovertebral angle tenderness. The temperature was 101.6 F, and blood pressure was 146/50. Diabetic retinopathy was noted. The urine showed 4+ sugar and 4+ acetone. There were 11,000 white blood cells per cu. mm., with a shift to the left. Blood sugar was 262 mg. per 100 cc., and serum amylase, 275 Somogyi units, Total cholesterol was

1226 mg. per 100 cc., with 720 mg. per 100 cc. in the esterified form. The patient required 620 units of insulin in the first 13 hours. She remained febrile for a few days, with gradual decreasing abdominal tenderness. A gall-bladder series showed normal function, with no evidence of calculi. She was discharged on the 17th hospital day on an insulin dosage of 10 units daily.

CASE 6.—In 1954, a 58-year-old Puerto Rican woman was known to have had diabetes for four years, but she had not required insulin. She entered the hospital with severe right upper quadrant and periumbilical pain of six hours' duration, associated with vomiting. Two weeks before she had had a similar episode lasting one day. On admission she appeared dehydrated and acutely ill. Her temperature was 98.6 F, with normal pulse and respiratory rates and a blood pressure of 155/85. There was marked abdominal tenderness, greatest in the right upper quadrant, where rebound tenderness was elicited. One hour after admission no bowel sounds were audible. Urine examination revealed 4+ sugar and 1+ acetone. White blood cell count was 21,000/cu. mm., with 84% polymorphonuclear leucocytes. Blood sugar was 445 mg. per 100 cc., and CO_2, 39 vol. %. Serum amylase was 188 Somogyi units on admission and rose to 350 units the following day. The patient received small doses of insulin and intravenous fluids. She was given antibiotics but continued to have fever. The gall bladder was not visualized on cholecystography. Eight days after admission exploratory laparotomy was carried out. The findings at operation included extensive peritoneal fat necrosis, a firm and slightly nodular pancreas, a small fibrotic gall bladder without stones, a cholecystoduodenal fistula, and a dilated common bile duct containing stones. A cholecystectomy, common-duct exploration, and transduodenal sphincterotomy were performed. Convalescence was uneventful, and the patient was discharged from the hospital 10 days after operation.

CASE 7.—A 54-year-old Negro woman was known to have had diabetes for nine years and was maintained on 45 units of isophane (NPH) insulin daily. She entered the hospital in 1954 because of an infected blister on the dorsum of the right foot. She had been hospitalized previously for eye operations, at which time she developed gross hematuria after catheterization. Examination revealed the infected foot, which was treated with incision and drainage and parenteral antibiotics. Ten days after admission the patient developed nausea, vomiting, epigastric pain, and lethargy. The blood pressure fell to 90/60 from an admission level of 150/90. The blood urea nitrogen was 88 mg. per 100 cc., compared with 22 mg. on entrance. Following several catheterizations the urine became grossly bloody, and the patient was noted to have slight right costovertebral angle tenderness. Examination of the urine revealed innumerable red and white blood cells and 2+ to 3+ albuminuria. The serum amylase was normal. After administration of intravenous fluids the blood pressure rose and blood urea nitrogen fell. The patient then became confused and semistuporous. The blood pressure fell again to shock levels, and the abdomen was diffusely tender with no bowel sounds. An electrocardiogram was normal. The blood sugar rose to 500 mg. per 100 cc., compared with a level on admission of 136 mg. A terminal white blood cell count showed a polynucleosis with marked left shift. The patient died three and one-half weeks after admission. Postmortem examination revealed marked reddening of the pancreas, with numerous areas of submucosal hemorrhage in the main pancreatic duct. Microscopic section showed marked congestion, hemorrhage, interstitial inflammation, necrosis, and fat necrosis. There was marked arteriolosclerosis of the pancreatic vessels. There were also hemorrhagic cystitis, acute pyelonephritis, and acute duodenal ulcer.

CASE 8.—In 1954, E. Gr., a 48-year-old white woman, was known to have had diabetes for 18 years and was maintained on 35 units of insulin daily. She developed an upper respiratory infection nine days before admission with a temperature of 101 F, nausea, and vomiting, for which she had been hospitalized elsewhere. Examination there revealed costovertebral angle tenderness and oliguria. The urine showed pyuria, hematuria, and albuminuria, with moderate glycosuria and acetonuria. The blood sugar was 360 mg. per 100 cc.; urea nitrogen, 75 mg. per 100 cc., and CO_2, 34 vol. %. She was treated with antibiotics, but oliguria persisted, and the patient developed singultus, vomiting, and confusion. On admission to this hospital she was acutely ill and confused. The temperature was 98 F; pulse rate, 85; respirations, 35, and blood pressure, 85/45. There was bilateral costovertebral angle tenderness with guarding and tenderness of both upper abdominal quadrants. The liver edge was palpable 3 fingerbreadths below the costal margin. Examination of the urine revealed a trace of sugar, no acetone, a trace of albumin, and a few red and white blood cells. The blood sugar was 540 mg. per 100 cc.; urea nitrogen, 304 mg. per 100 cc., and CO_2, 6 vol. %. She received 1/6 molar lactate intravenously, with a rise in the CO_2 to 37 vol. %, and her urinary output increased to 2600 cc. She then was given intravenous fructose in water alternating with fructose in saline and excreted 10 liters of urine on the second hospital day. At this time she had an episode of hematemesis requiring transfusion of 1 liter of blood. The following day her temperature rose to 104F; she had convulsions, lapsed into coma, and died. Prior to death, urine examination revealed 2+ to 4+ glycosuria without acetonuria. Post-

mortem examination revealed numerous areas of peritoneal fat necrosis. The pancreas appeared normal grossly, but on microscopic section there was dilatation of all the ducts, which were filled with inflammatory cells, and there were large areas of fat necrosis. The kidneys were normal in size and showed moderate congestion of the glomeruli, some hyaline casts, and increased mitoses in the tubular cells. The liver was fatty.

COMMENT

The salient features of the eight patients included in this report are presented in the Table. All were known diabetics, the diabetes ranging in duration from 6 months to 18 years, averaging 7.3 years. Five had required insulin during the period immediately prior to the onset of acute pancreatitis. Only two had never used insulin. The age of the patients ranged from 20 to 62 years, with an average age of 43. All the patients were women. This sex preponderance has not been noted in cases previously reported: Of 15 patients whose sex was mentioned, 7 were male and 8 were female.¶ The sex distribution in a series of 250 nondiabetics with pancreatitis was 53.6% females.[16]

The mortality rate among the patients in this report was significantly higher than that in a nondiabetic group hospitalized during the same period. Of the diabetics, six of eight died. Of 98 nondiabetics with severe acute pancreatitis, 25 died. The excessively high mortality in diabetic patients has been observed in all reports and cannot be correlated with the anatomical lesions, which are not particularly severe. The statement has been made that "when a diabetic patient is attacked by acute pancreatitis the diagnosis is grave indeed." [16]

The low incidence of correct clinical diagnosis in the present group of cases and in others is striking. Warren and co-workers state that acute pancreatitis in a known diabetic is always difficult to detect.[17] Of the six fatal cases reported here, pancreatitis was suspected in none before death. This is partially due to the lack of definitive abdominal symptoms and signs. While abdominal pain was noted by six of eight patients, abdominal tenderness was described in only four instances, diffusely located in the upper abdomen, and rebound tenderness was elicited in only two of these patients, both of whom survived. However, there was no patient who did not have either abdominal pain or some positive abdominal findings on examination.

Diabetic coma was present in four of the six fatal cases and in one of the two patients who survived. Death occurred within the first 24 hours of admission in three comatose patients whose course was fulminating. The possible presence of acute pancreatitis should therefore be considered when patients complain of abdominal pain during episodes of diabetic acidosis.[17] As Root has indicated, shock and resistance to therapy, combined with abdominal and/or back pain are suggestive of acute pancreatitis as the precipitating factor for diabetic coma.[6]

The present group of patients showed concomitant evidence of renal involvement, clinically and pathologically, in four of the eight. Patients 1, 4, and 8 manifested varying degrees of oliguria and anuria. All three were in diabetic coma. Patient 8 was actually treated for renal shutdown and subsequently underwent massive diuresis. At autopsy, examination of the kidneys of these patients revealed tubular degeneration, swelling, and increased mitoses. Patient 5 had costovertebral angle tenderness associated with gross hematuria, pyuria, and albuminuria attributable to a hemorrhagic cystitis and acute pyelonephritis. Lynch [18] recently reported five nondiabetic patients who had "nephrosis" discovered at autopsy in association with acute pancreatitis. Detailed clinical records, however, including blood pressure and urinary output, were not presented.

While the occurrence of acute pancreatitis in patients with diabetes is striking, no satisfactory explanation of the underlying mechanism is readily available. The presence of concomitant biliary tract disease was noted in only one patient, and another was an alcoholic. It is well accepted that long-

¶ References 3, 6, 8, 10, and 11-14.

Clinical Data in Eight Patients with Diabetes and Pancreatitis

Patient	Age, Yr.	Sex	Duration of Diabetes	Insulin	Abdominal Symptoms	Abdominal Signs	Diagnosis Made	Coma	Outcome	Remarks
1. E. Ga.	20	F	6 mo.	No	Severe upper abd. pain 24 hr.	None	No	Yes	Died, 12 hr.	Associated hyperlipemia; terminal shock and anuria
2. R. C.	62	F	12 yr.	Yes	Severe epigastric pain → back, 1 day	3 FB liver	No	No	Died, 6th day	Clinical diagnosis of acute myocardial infarction; shock a prominent feature
3. E. G.	49	F	8 yr.	40 units PZI, 4 mo.	Dull epigastric pain 3 wk.	None	No	Yes	Died, 20 hr.	Shock and insulin resistance
4. M. H.	29	F	5+ mo.	No	None	Diffuse rigidity	No	Yes	Died, 12 hr.	Terminal pulmonary edema, oliguria
5. H. L.	46	F	7 yr.	8-15 units PZI	Recurrent upper abd. pain, 3 days	Tenderness and rebound in upper abdomen	Yes	Yes	Recovered after 17 days	Elevated serum amylase; gall bladder series normal; marked hypercholesteremia
6. M. R.	58	F	4 yr.	No	RUQ and periumbilical pain, 6 hr.	Marked tenderness and rebound, RUQ	Yes	No	Laparotomy 8 days after admission; recovered	Elevated serum amylase; associated biliary tract disease
7. G. S.	54	F	9 yr.	45 units isophane insulin	Epigastric pain	Diffuse tenderness, absent bowel sounds	No	No	Died 2 wk. after onset	Associated shock, hematuria; marked arteriosclerosis in pancreatic vessels
8. E. Gr.	48	F	18 yr.	35 units	None	Tenderness and guarding, both upper quadrants	No	Yes	Died 12 days after onset	Initial oliguria followed by massive diuresis

standing diabetes is associated with degenerative vascular disease, and perhaps local involvement of the pancreatic vessels might be incriminated. In only one patient was marked arteriosclerosis of the pancreatic vessels noted at autopsy. The possibility remains that some lesion of the smaller arterioles or capillaries exists which is not recognized or that functional ischemia of the pancreatic tissue is present despite the lack of demonstrable anatomical lesions. The importance of ischemia as an etiological factor in pancreatitis has been brought forward by Rich and Duff [11] and by Block, Wakim, and Baggenstoss.[19]

In addition, it is possible that in at least two instances where marked hypercholesteremia was noted (Patients 1 and 5) we may have been dealing with the association of idiopathic hyperlipemia and diabetes mellitus.[20] The increased incidence of acute pancreatitis in patients with idiopathic hyperlipemia has been ascribed to fat emboli in the pancreatic vessels.[21]

SUMMARY AND CONCLUSIONS

Eight instances of acute pancreatitis in patients with known diabetes mellitus were encountered among one hundred six patients with acute pancreatitis hospitalized from 1936 to 1954.

The average duration of antecedent diabetes was 7.3 years. Six patients had required insulin therapy.

All patients were female, contrary to the fairly equal sex distribution reported elsewhere in both diabetics and nondiabetics with pancreatitis. The average age was 43 years.

An excessively high mortality (6 of 8) was noted in diabetics as compared with nondiabetics (24 of 98.) In none of the fatal cases was the correct clinical diagnosis made. Except for pain, abdominal symptoms and signs were not striking, but one or another was present in all. Diabetic coma was present in five patients, four of whom died—three within 24 hours.

Oliguria or anuria occurred in three patients in diabetic coma and was associated with renal tubular lesions. A fourth fatal case had acute pyelonephritis.

A possible vascular etiology is proposed for the occurrence of acute pancreatitis in patients with known diabetes mellitus.

The diagnosis of acute pancreatitis should be especially considered in diabetics who present coma resistant to therapy, with abdominal pain or tenderness, shock, or oliguria.

REFERENCES

1. Warren, S., and Le Compte, P. M.: The Pathology of Diabetes Mellitus, Philadelphia, Lea & Febiger, 1952, pp. 68-69.

2. Sprague, R. G.: Diabetes Associated with Chronic Relapsing Pancreatitis, Proc. Staff Meet. Mayo Clin. **22**:553-558 (Nov. 26) 1947.

3. Shumacker, H. B., Jr.: Acute Pancreatitis and Diabetes, Ann. Surg. **112**:177-200, (Aug.) 1940.

4. Rodriguez, J.: Acute Pancreatitis with Fat Necrosis, Complicated by Diabetic Coma, J. A. M. A. **82**:203-204 (Jan. 19) 1924.

5. Steiner, M. M., and Tracy, P. C.: Diabetic Coma, Acute Pancreatitis and Bacillus Welchii Peritonitis, Am. J. Dis. Child. **65**:36-45 (Jan.) 1943.

6. Root, H. F.: Diabetic Coma and Acute Pancreatitis with Fatty Liver, J. A. M. A. **108**:777-780 (March 6) 1937.

7. Rose, T. F.: Pancreatitis at the Royal North Shore Hospital of Sydney from 1925 to 1950, M. J. Australia **2**:453-458 (Oct. 6) 1951.

8. Bowers, J. Z., and Atkins, J. L.: Acute Pancreatitis with Diabetic Acidosis Occurring in the Course of Diabetes Mellitus, Bull. School Med. Univ. Maryland **26**:234-240 (April) 1942.

9. Ivy, A. C., and Gibbs, G. E.: Pancreatitis: A Review, Surgery **31**:614-642 (April) 1952.

10. Foord, A. G., and Bowen, A. D.: Acute Interstitial Pancreatitis in 2 Cases of Diabetic Coma, Am. J. M. Sc. **180**:676-681 (Nov.) 1930.

11. Rich, A. R., and Duff, G. L.: Experimental and Pathological Studies on the Pathogenesis of Acute Hæmorrhagic Pancreatitis, Bull. Johns Hopkins Hosp. **58**:212-259 (March) 1936.

12. Cullen, T. S., and Friedenwald, J.: Acute and Chronic Pancreatitis: Clinical Observations, Arch. Surg. **15**:1-29 (July) 1927.

13. Felsenreich, F.: Klinik der akuten und subakuten Pankreasnekrose, Arch. klin. Chir. **168**:307-348, 1932.

14. Cabot Case 16282, New England J. Med. **203**:82-85 (July 10) 1930.

15. Beck, D.: Acute Pancreatitis, J. Mt. Sinai Hosp. **4**:895-922 (March-April) 1938.

16. Fallis, L. S.: Acute Pancreatitis: Observations on 250 Cases, J. Internat. Coll. Surgeons **16**:337-341 (Sept.) 1951.

17. Warren, K. W.; Fallis, L. S., and Barron, J.: Acute Pancreatitis and Diabetes, Ann. Surgery **132**:1103-1110 (Dec.) 1950.

18. Lynch, M. J.: Nephrosis and Fat Embolism in Acute Hemorrhagic Pancreatitis, A. M. A. Arch. Int. Med. **94**:709-717 (Nov.) 1954.

19. Block, M. A.; Wakim, K. G., and Baggenstoss, A. H.: Experimental Studies Concerning Factors in the Pathogenesis of Acute Pancreatitis, Surg. Gynec. & Obst. **99**:83-90 (July) 1954.

20. Adlersberg, D., and Wang, C. I.: Syndrome of Idiopathic Hyperlipemia, Mild Diabetes Mellitus and Severe Vascular Damage, Diabetes **4**:210-218 (May-June) 1955.

21. Klatskin, G., and Gordon, M.: Relationship Between Relapsing Pancreatitis and Essential Hyperlipemia, Am. J. Med. **12**:3-23 (Jan.) 1952.

Treatment in Internal Medicine

THE TREATMENT OF LEPROSY

R. G. COCHRANE, M.D., F.R.C.P., D.T.M.& M.,
London

NO CENTURY in the history of medicine has seen such revolutionary changes in our conception of disease, especially in the realm of treatment, as has the twentieth century, particularly in the last 30 years. New discoveries have given rise to fresh approaches to diseases which hitherto were considered incurable, and many of these diseased conditions have surrendered to the combined forces of applied physiology, biochemistry, and experimental and clinical medicine. Within the last 35 years diabetes, pernicious anemia, bacterial endocarditis, septicemia, plague, typhus, and malaria have all come within the realm of curable diseases. Even in the more chronic infective conditions, such as tuberculosis and leprosy, there is a hope and an expectation of cure, which has never been experienced before. It is, therefore, with the sense of one treading on the verge of a new world that I approach this subject of leprosy and acknowledge the honor and privilege of being asked to present the over-all therapeutic picture of this disease.

Before one endeavors to outline the new approach to the therapy of leprosy one must attempt to explain something of the nature of the disease which is being considered. Unless there is some understanding of this, the therapy will be that of a person who can read a chart but who is unaware of the pitfalls and dangers of the path which he has elected to explore. Antibiotics and chemotherapeutic agents and substitutionary endocrine treatment are all means by which mankind enters into new experiences of health, but to have the knowledge that these "wonder" remedies exist, and not to appreciate the complexities of the diseases or dysfunctions themselves, is to be like one who has the key and will to open the gate into the Garden Beautiful but in whose hands there is no strength to turn the lock!

Leprosy, like its sister disease tuberculosis, has many manifestations, and has in some respects a greater tendency to self-healing; the sequelae of the disease frequently need the skill and understanding of the surgeon and physiotherapist rather than the expert knowledge of the internist. Khanolkar,[1] stimulated by the work of the Continental workers, early in this century, and encouraged by the recent advances in and the outstanding contributions to the study of leprosy in Calcutta, Madras, and Bombay, has shown that leprosy is neural in its inception and that a correct understanding of the pathology of the disease can best lead to wise and successful treatment.

Evidence is accumulating to show that probably the usual method of infection is for Mycobacterium leprae to enter into the skin of a healthy person, particularly a child. To anyone who has studied the conditions in areas where leprosy is endemic, watching the constant contact of children with an infective case, it is not difficult to appreciate how this "rubbing in" of M. leprae is achieved. Once the organism gets into the skin, it appears to make its way to the axon-plasma filaments—the ultimate terminals of the nerves to the skin. From here M. leprae enters the axis cylinder and, probably by multiplication, gradually ascends the nerve. Khanolkar [2] (1955) has shown that bacilli form in the axis cylinder "intercalated swellings," and Gault and co-workers [3] have confirmed by histochemical methods the probability of bacilli being in the axis cylinder of the nerve. In the ma-

Submitted for publication Nov. 16, 1955.

Technical Medical Adviser, American Leprosy Missions; Adviser in Leprosy, Ministry of Health (London).

jority of instances, if pathological lesions of leprosy develop, the M. leprae organisms "burst" out from the axis cylinder into the corium of the skin, and the type of leprosy which develops has a direct relationship to the type of cellular response stimulated by the presence of M. leprae. It is, therefore, advisable, before therapy is discussed in detail, to consider the immunological approach to leprosy.

There appear to be three different types of tissue response in leprosy: (1) a state or potential state of hypersensitivity, (2) a state in which the tissues are desensitized, and (3) an unstable, intermediate state of partial sensitivity. These tissue responses are indicated by the lepromin reaction. In the first state this is strongly positive; in the second, absolutely negative, and in the third, weakly positive or negative. Further, these defensive responses show themselves in the clinical lesions, which have been divided into tuberculoid, lepromatous, and dimorphous (borderline) leprosy, with their characteristic clinical, histological, and immunological manifestations. The following diagram gives in outline my conception of their classification.

Indeterminate

Macular lesions		Polyneuritic lesions
Tuberculoid	Dimorphous (Border-Line)	Lepromatous
Macular lesion (Maculo-anesthetic)	Macular lesion	Macular lesions Preleproma Leproma
Infiltrated lesion Minor Major	Infiltrated lesion Atypical tuberculoid Atypical lepromatous	Infiltrated lesion Diffuse Nodular
Polyneuritic	Polyneuritic	? Polyneuritic

The chief difference between this outline of classification and the one accepted in Madrid is the narrowing down of the indeterminate group by not including the prelepromatous macular lesions or the dimorphous macular lesions. The latter have not been accepted as occurring by most leprologists. It is not within the purposes of this contribution to give a detailed account of the clinical manifestations of this disease, but the above description is by way of introduction to the question of treatment.

TREATMENT

Owing to an unfortunate misinterpretation of a Biblical word, the disease now known as leprosy has been confused with a Biblical concept signifying one who is defiled or blemished. While this misconception of a theological idea created an interest in leprosy and a devotion to the cause that little else could do, it must now be clearly stated that modern-day leprosy has no connection with the word *tsaraath* of the Old Testament writings.

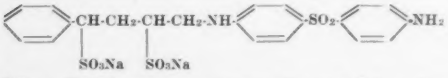
Today, with the advent of the sulfone treatment for leprosy, much interest has been created in therapy, for it is now realized that, given wise application of sulfone treatment and attention to auxiliary methods, it is possible to control leprosy as an endemic disease.

The brief history of sulfone therapy illustrates well the necessity for cooperation between the bacteriologist, biochemist, clinician, and pharmacologist if success is to be attained in the conquest of disease.

Diaminodiphenylsulfone (DDS; Dapsone) (structural formula: NH_2-C$_6$H$_4$-SO_2-C$_6$H$_4$-NH_2) has been known since 1908. As a result of the pioneer work of Feldman [4] in America, Rist [5] in France, Buttle [6] and Brownlee [7] in Britain, and Faget [8] and his colleagues at Carville leading up to the trial of glucosulfone sodium (Promin)—a disubeffective therapeutic weapon. It was felt ized that this group of drugs had a powerful action on M. leprae and appeared to be an effective therapeutic weapon. It was felt by workers in India that unless a cheaper form of the drug became available this new and effective therapeutic agency could not

reach the mass of the persons suffering from leprosy. Workers, therefore, concluded that efforts must be made to reduce the cost of the treatment. Cochrane,[9] in 1949, seeing the work of Francis in veterinary medicine, was encouraged to try the parent sulfone. At the same time, he experimented with the use of tetrasodium 1,1'(sulfonylbis[*p*-phenyleneimino]bis(3-phenyl-1,3-propanedisulfonate) (Sulphetrone) parenterally, both in oil suspensions and in a 50% solution. It should be noted that Dharmendra and Chatterjee[10] about this time also used by injection a 3.3% solution of Sulphetrone made by crushing up tablets and dissolving them in water.

As a result of the work of Lowe* in Africa, it was realised that the mother-sulfone (diaminodiphenylsulfone [DDS]) could be given by mouth. It was claimed by some workers that DDS was the only suitable drug[2] to give, because all disubstituted diaminodiphenylsulfones were broken down into the parent sulfone. Cochrane[13] confirmed, with the help of Bushby, that while sulfones by mouth were broken down to DDS by hydrolysis, Sulphetrone, particularly in a 50% aqueous solution when given parenterally, was not broken down but was converted into a monosubstituted diaminodiphenylsulfone with the following formula:



Thus Sulphetrone parenterally acted by virtue of the fact that one amino acid group was freed; i. e., it was made active by virtue of the fact that it was broken down to a monosubstituted derivative. All sulfone derivatives, therefore, appear to act either because they are broken down to the parent sulfone or by virtue of the fact that they are converted into a monosubstituted derivative. It would seem, therefore, reasonable to give as a routine treatment either DDS or one of the disubstituted diaminodiphenyl sulfones, which are converted to a monosubstituted product in the tissues. The parent sulfone, however, is apparently detoxicated in the liver and in consequence is liable to be more toxic than those compounds which are not so changed. However, it is cheap and easily administered, and therefore it has become the drug of choice in the routine treatment of leprosy.

The treatment of leprosy is not just a matter of giving sulfones in the correct dosage but is also one of adjusting the dose to the type and activity of the disease, so that untoward and sometimes damaging reactions may be avoided.

As a general rule, it is wise to proceed cautiously in all forms of sulfone therapy. I will, therefore, first outline the course of treatment with the parent sulfone (diaminodiphenylsulfone) by mouth and then indicate the dosage regimen used with other sulfones. It has to be remembered that physicians will use the product which is most easily available.

Dosage and Administration

It is advised to commence at 25 mg. DDS twice a week. At the end of 14 days the dosage is increased to 50 mg. twice a week, and then at similar intervals it is increased by 25 mg. increments until 100 mg. twice a week is reached. The dose then is raised by 100 mg. every month until 300 mg. twice a week is given. When this dosage is reached, if more convenient, one tablet may be given every day, missing out Sundays.

When oral administration of DDS is not convenient or for some reason is contraindicated, then sulfone in the form of a 50% aqueous solution of Sulphetrone should be given, starting at 0.5 cc. twice a week, increasing by 0.5 cc. increment in 14 days and then by 1 cc. increments each month until a dosage of 3 cc. twice a week is reached. Children from 12 to 15 years of age should receive three-quarters of the adult dose; those from 7 to 12 years of age, half the adult dose, and those under 7 years of age, one-quarter of the adult dose.

In the United States, glucosulfone sodium (Promin) and sulfoxone sodium U. S. P. (Diasone sodium) are largely given. Both are disubstituted diaminodiphenyl sulfones and are probably broken down to the parent

* References 11 and 12.

substance. Glucosulfone sodium is given intravenously daily. The generally recommended dosage in adult patients in good general condition and with a normal blood picture is an initial dose of 2 gm. in 5 cc. of solution given intravenously daily. This dose is increased after one or two weeks by 1 cc. daily until a dose of 12.5 cc. is reached. The dosage for children depends on age, weight, general physique, and individual tolerance. The drug should be administered daily for from one to three months, followed by a rest period of from one to two weeks, after which treatment is resumed. The dosage and the length of the rest periods may be modified in accordance with the requirements of the individual patient. But I consider this dosage is somewhat excessive.

When sulfoxone sodium is preferred, the following dosage is suggested:

1st wk.: 0.3 gm. (1 tablet) daily for 6 days; 1 day of rest
2d wk.: 0.6 gm. (2 tablets) daily for 6 days; 1 day of rest
3d wk.: 0.9 gm. (3 tablets) daily for 6 days; 1 day of rest

The maximum dose recommended for the adult is three tablets per day (0.99 gm.). As one-third of the molecule of sulfoxone sodium is hydrolysed to DDS when given by mouth, this dosage, over a period of six days, would be 1.98 gm. per week, or almost equivalent to 2 gm. (2000 mg.) of the parent sulfone. This, in my opinion, is too high; a maximum of not more than two tablets need be given, and in many instances, e. g., in severe lepromatous cases or for adult persons of slender build (140 lb.), one tablet a day for six days a week should be sufficient.

Toxicity and Side-Effects

It must be remembered that the parent sulfone, DDS, is a toxic substance and that it is detoxicated in the liver. This knowledge need not cause undue concern, but neither should one assume an indifferent attitude in this regard; for toxicity, if it occurs, is of serious moment. Provided there are slow increments and the dosage is kept within the above limits, no serious toxic results are likely. The chief toxic effects are (1) anemia, (2) dermatitis, (3) hepatitis, and (4) psychosis. The most frequent side-effect is anemia, and occasionally dermatitis occurs, which may be exfoliative, but persons of good nutrition and mental stability are unlikely to show the more serious evidences of toxicity. Any derivative which is broken down to DDS is liable to be more toxic than those which are not so converted. This means that if there are signs of toxicity then the drug should be stopped and parenteral Sulphetrone should be substituted. The latter, by virtue of the fact that it is converted not into a disubstituted but into a monosubstituted diaminodiphenylsulfone, is not toxic, and apart from causing a mild dermatitis Sulphetrone parenterally is, in my experience, nontoxic; those who have used it extensively have confirmed this observation.

Reactions in Leprosy

It is impossible, in the space available, to give a detailed account of reactions in leprosy, but in view of the fact that they are liable to be precipitated by treatment, particularly when the parent sulfone and those derivatives which are broken down to the basic substance are used, physicians treating leprosy should have some appreciation of the management of these conditions.

Reaction states must be differentiated from activity of the disease. Reactions in leprosy are sudden exacerbations of the disease of varying severity as a result of an attempt by the tissues to limit the spread of the disease or to check it entirely. These tissue reactions have been divided into those which are manifestations of a successful defense, those which indicate an inability of the tissues to limit the spread of the disease, and, lastly, those which produce a state of unstable equilibrium in the host-parasite relationship; these three defensive states are seen in tuberculoid, lepromatous, and dimorphous (border-line) cases. The whole question of reaction demands a discussion on host-tissue response in leprosy, and space does not allow of detailed description of this. In tuberculoid reactive conditions and in border-line cases the generally accepted rule is to stop all specific treatment; the reaction itself is favorable, for it hastens the resolution of the dis-

ease, but the consequences of the reaction, in the form of residual deformity, are serious, and, therefore, all possible steps to prevent this should be taken. Too little attention is sometimes given to this aspect of leprosy, on the assumption that as long as sulfones are being given all is well.

Lepromatous reaction is difficult to treat. Generally speaking, when it is acute (erythema nodosum phenomenon) all treatment is stopped. The stand-by in the treatment of the acute reacting phases in leprosy—the so-called erythema nodosum phenomenon—is one of the antimony products. Antimony potassium or sodium tartrate may be given in doses every other day—three doses of 0.02 gm. intravenously, followed by three doses of 0.04 gm. by the same route. The newer preparations, such as stibophen (B. W. & Co.) (Fantorin; Glaxo) or lithium antimony thiomalate (Anthiomaline; M. & B.) can be given, at first 1 cc. every other day for six doses and then 2 cc. every other day. These preparations can be given intramuscularly or deep subcutaneously.

When these remedies fail and the acute reaction phases continue, then the careful administration of cortisone or corticotropin should be tried, but it is not given in excessive dosages (not more than 100 mg. per day) and is balanced by sulfone therapy. In other words, that amount of cortisone is given which will keep the patient comfortable and enable him gradually to reach a therapeutic dose of DDS or one of the sulfone derivatives. When a dose of 100 mg. twice a week of DDS (or 0.5 cc. twice a week parenterally of Sulphetrone) is reached, the cortisone is then gradually reduced. Long-acting corticotropin may be a safer remedy, but I have as yet no experience of this. This low dosage of sulfone is maintained for six months before any attempt is made to increase the dose.

Reaction phases in leprosy must be differentiated from periods of acute exacerbation of the disease, in which the bacilli appear to multiply rapidly and fresh lesions containing enormous numbers of bacilli appear, existing lesions become more active, and the whole disease process rapidly extends. Under such circumstances cortisone therapy is contraindicated. Along with these acute exacerbations, however, erythema-nodosum-like reactions may be superimposed. Under these circumstances, one might have to resort to cortisone, but this should only be used if no other treatment will relieve the symptoms of disease.

Criteria of Discharge and Action of the Sulfones

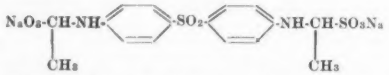
The question is constantly being raised, "Are sulfones curative or suppressive, and how long must therapy be maintained after all activity has ceased?"

In the first place, one has to remember that the sulfones are not bacteriocidal; they are bacteriostatic. They act, probably, as other chemotherapeutic agents, by depriving the bacillus of one of the essential amino acids (*p*-aminobenzoic acid), and they produce a tissue environment which inhibits multiplication of M. leprae. The final "cure" of leprosy depends on whether the macrophages of the tissue are able ultimately to deal with the viable remnants of M. leprae. If this is not possible—and one assumes that a certain number of persons are unable to deal the final death blow to the bacillus—these persons are, therefore, in danger of relapse. A reasonably safe rule in nonlepromatous leprosy is to continue treatment for 18 months or for 1 year after all activity has ceased, whichever is longer. In lepromatous cases many authorities consider that treatment should be continued for life, but in any case it should be continued for not less than two years after activity of the disease has ceased. It is assumed that the technique for assessing whether this stage has been achieved is good; for slipshod or careless techniques will lead to disappointment. The technique of Wade is recommended.

Additional Remedies

It will naturally be asked whether there are any other drugs which are effective in leprosy. It may be said that up to now no drugs have been discovered which replace

the sulfones in their efficacy. Some years ago a soluble form of DDS, in reality a disubstituted diaminodiphenylsulfone, disodium 1, 1′ (sulfonylbis [*p*-phenyleneimino]) bisethanesulfonate, which originally went under the code number M.2196, was introduced by I.C.I.† and is now available as Soluble Avlosulphone. The formula of this drug is as follows:



This derivative is broken down to the parent sulfone, and 1 ml. is equivalent to 200 mg. of DDS.

It has been shown that in cases where reactions are troublesome amithiozone (4-acetylaminobenzal thiosemicarbasone) is useful in tiding over periods of reaction, but this drug should not be used for more than 18 months. The commencing dosage is 25 mg. per day, to be increased each fortnight by 25 mg. until a maximum of 150 mg. is reached. Lowe [14] has shown that at the end of two to two and one-half years resistance apparently develops.

Isonicotinic acid should not be used alone, for Hale and Molesworth † have produced evidence suggesting that isoniazid (isonicotinic acid hydrazide; I. N. H.), if used alone and not combined with sulfones, increases the resistance of the bacilli, not only to isoniazid but also to subsequent sulfone therapy. This apparent antagonism between isoniazid and the sulfones has, as yet, not been confirmed by other workers.

Hydnocarpus or Chaulmoogra Oil and/or Esters.—It is generally assumed that there is now no place for these older remedies and that sulfones have replaced the necessity for hydnocarpus oil. There is evidence, however, to suggest that there is some logic in combining sulfone therapy with the intradermal administration of Chaulmoogra or Hydnocarpus esters. There is, in my opinion, no advantage in combining sulfone in suspension with hydnocarpus oil. It is claimed that when sulfones are suspended in hydnocarpus oil DDS is more slowly absorbed, but my experience has been that sulfones suspended in hydnocarpus oil are more difficult to inject and that the injection tends to be painful, and in both media the reactions appear to be more frequent. If hydnocarpus oil or esters are given, they should be used intradermally, all bacillary-positive areas of the skin being systemically given intradermal injections. The dose of hydnocarpus esters should not be less than 5 cc. twice a week. I have stated elsewhere that it appears that unless the M. leprae organisms multiply in the skin progressive disease seems impossible of development. Intradermal injections are tedious and tend to be painful, and, therefore, unless the patient is willing and the doctor confident, these should not be given, but reliance should be placed on sulfones alone.

Ancillary Treatment.—It must be ever borne in mind that leprosy is a disease which deforms and mutilates, and, up to recently, it has been asuumed that under certain conditions deformity in leprosy was inevitable. Work during the last 8 to 10 years, however, has shown not only that deformity is not inevitable, but that all deformity, if the disease is treated in time, can be prevented, and much can be relieved by modern orthopedic and physiotherapeutic measures. The two pioneer workers in this realm are Dr. Paul Brand, in India, and Dr. Reardon, in New Orleans. Mention is made of these advances, for they mean that not only has leprosy come within the range of more effective treatment but many of its most distressing sequelae can be prevented or relieved completely.

COMMENT

Looking back more than 30 years, I have seen advances in the treatment, management, and prevention of leprosy as great as in any other disease, and it is increasingly realised that, whether viewed from the clinical, pathological, Public Health, or research aspects, leprosy is a specialty which not only can become an all-absorbing one but which will bring dividends in contentment and personal

† Imperial Chemical Industries Ltd.

† Molesworth, D., and Hale, J.: Personal communication to the author, 1955.

satisfaction of great value, to the lasting benefit of Mankind, which, after all, is the ultimate goal of Medicine.

REFERENCES

1. Khanolkar, V. R.: Indian Council of Medical Research, Special Report Series, No. 19, New Delhi, 1951, p. 13.

2. Khanolkar, V. R.: Indian J. M. Sc. **9**:28, 1955.

3. Gault, E. W.; Jayaraj, A. P., and Gass, H. H.: The Application of Histochemical Methods in the Study of the Skin in Leprosy, Internat. J. Leprosy, to be published.

4. Feldman, W. H.; Hinshaw, H. C., and Moses, H. E.: Am. J. Path. **17**:578, 1941.

5. Rist, N.; Bloch, F., and Hamon, V.: Compt. rend. Soc. biol. **130**:976, 1939

6. Buttle, G. A. H.; Stephenson, D.; Smith, S.; Dewing, T., and Foster, G. E.: Lancet **1**:1331, 1937.

7. Brownlee, G.; Green, A. F., and Woodbine, M.: Brit. J. Pharmacol. **3**:15, 1948.

8. Faget, G. H., and others: Pub. Health Rep. **58**:214, 1943.

9. Cochrane, R. G.; Ramanujam, K.; Paul, H., and Russell, D.: Leprosy Rev. **20**:4, 1949.

10. Chatterjee, S. N.: Leprosy India **21**:81, 1949.

11. Lowe, J.: Lancet **1**:145, 1950.

12. Lowe, J.: Lancet **1**:18, 1951.

13. Cochrane, R. G.: Brit. M. J. **2**:1220, 1952.

14. Lowe, J.: Leprosy Rev. **25**:186, 1954.

Progress in Internal Medicine

SYPHILIS

Review of the Recent Literature

HERMAN BEERMAN, M.D.
IRA L. SCHAMBERG, M.D.
LESLIE NICHOLAS, M.D.
and
MARVIN S. GREENBERG, M.D., Philadelphia
With the Collaboration of T. Guthe, M.D., and
C. J. Hackett, M.D., Geneva, Switzerland

DURING July 1, 1954, to July 1, 1955, the interval covered by this 20th annual review of syphilis, the status of this disease as an important health problem was still in a state of flux. The indications are that the trend to relegate syphilis to limbo is growing, in spite of the evidence produced by the "die hards" that late syphilis is an ever-increasing problem and that there are many urgent current needs that demand attention to the actual control of this disease (Shaffer [1] and editorial, *American Journal of Public Health* [2]). As mentioned in the previous review,[3] the *American Journal of Syphilis, Gonorrhea and Venereal Diseases* is to be replaced by the *Journal of Chronic Diseases;* it is with a note of sadness that Joseph Earle Moore,[4] who has been the editor of the *American Journal of Syphilis, Gonorrhea and Venereal Diseases* since October, 1935, records the fact that the November, 1954, issue is the last issue of this publication. This journal, established thirty-nine years ago under the name of the *American Journal of Syphilis,* has played an honorable and influential part in the control of venereal diseases throughout the world. It has recorded new and basic laboratory discoveries and the revolutionary changes in treatment brought about by the antibiotic era as well as public health aspects of the venereal diseases. Decline in the incidence of syphilis, reduction in interest in the disease, and lessening of the volume of investigative studies so that worth-while manuscripts in sufficient number to fill its pages are unavailable have combined to sound this journal's death knell. It is pointed out that many basic problems relating to syphilis are still unsolved and that, if the incidence of the disease continues to fall, they may never be solved. It is pointed out that the *British Journal of Venereal Diseases* is now one of the few periodicals published in English devoted to this field. A hope is expressed that not only will our British colleagues keep the torch burning but that American investigators will send studies for publication to Britain, since science has no international boundaries. Moore hopes that the readers and friends of the *Journal* will think of it in Navy terminology as having completed a task "well done."

In an editorial in *The Journal of the American Medical Association,*[5] notice was taken of the effect of the decline in the incidence of syphilis. Just two months after Dr. Joseph Earle Moore announced the discontinuance of the *American Journal of Syphilis,* the chief editor [6] of the *A. M. A. Archives of Dermatology and Syphilology* announced that the word syphilology had been dropped from the title of the *Archives.* The reasons noted by Dr. O'Leary were (1) few dermatologists now have patients with syphilis, (2) the papers on syphilis now submitted to the *Archives* are few and far between, and (3) there are decidedly fewer patients with syphilis. Also, at this time when

Submitted for publication Oct. 6, 1955.

From the University of Pennsylvania Departments of Dermatology, School of Medicine (Donald M. Pillsbury, M.D., Professor) and Graduate School of Medicine (Herman Beerman, M.D., Chairman), and the Venereal Disease Control Section, Division of Preventive Medicine, Philadelphia Department of Public Health (John William Lentz, M. D., Chief). Dr. Guthe and Dr. Hackett are with the World Health Organization.

the incidence of syphilis is diminishing rapidly and when the teaching of syphilology is being deemphasized, it is of more than passing interest to the reviewers to note that a recent diagnostic problem in *The Journal of the American Medical Association* was a case of syphilitic aneurysm of the thoracic aorta.*

The journal *Science* [9] also makes passing comment about the spectacular progress against syphilis that followed the discovery of penicillin and the subsequent new problems and new dangers. These subjects are dealt with in a new 25-cent pamphlet, "Syphilis: The Invader" by Erik Barnouw and E. Gurney Clark, just published by the Public Affairs Committee, 22 E. 38th St., New York. The pamphlet was prepared in cooperation with the Center for Mass Communication, Columbia University Press, and is designed to accompany a new film, "The Invader." The many achievements of penicillin therapy are listed. Because of penicillin's effectiveness, most of the federally supported rapid treatment centers had been closed by 1951. But the authors warn that the syphilis problem is not resolved: 1. The rapid-treatment centers were an ideal setting for interviews by contact investigators, and the present local arrangements for follow-ups are too complex, which makes contact tracing more difficult. 2. A moderate quantity of penicillin, perhaps prescribed for some standard infection, will not cure syphilis and may hasten the disappearance of outward symptoms so that they pass unnoticed. 3. A decrease in the number of cases treated may not mean a decrease in the number who have syphilis, for the search for cases is being made on a far less sweeping scale than in previous years.

One of the major causes of the decline in syphilis incidence is penicillin therapy, which was first introduced in 1944. The World Health Organization [10] observed the 10th anniversary of the introduction of penicillin therapy for syphilis by devoting an entire issue of its bulletin to syphilis. The bulletin notes that although syphilis has become much less serious in some countries in the last 10 years it still is an important public health problem in many others. It is estimated that there are about 20,000,000 persons with syphilis in the world today and that in special areas of certain countries as much as 80% of the population may be affected. One article reports the wide variance found within countries in the prevalence of venereal syphilis. In Africa as a whole it ranges from 14.1% to 32.9%; in southeast Asia, from 0.6% to 31%; in Egypt, from 0.29% to 27%; in Ethiopia, from 4.2% to 82%; and in India, from less than 1% to 50%. Material submitted by the United States showed some of the economic loss in this country from syphilis in one recent year. Maintenance of patients suffering from syphilitic psychosis was set at $41,000,000; loss of income to this group, $86,000,000; loss in state and federal income taxes due to syphilitic psychosis, $6,000,000, and maintenance of blind syphilitics, $18,000,000. Rein [11] believes that penicillin alone is the treatment of choice in syphilis and gonorrhea when these are uncomplicated and he regrets the lowered index of suspicion on the part of physicians and believes that venereal disease may be eradicated if proper measures are taken.

On the other hand, it is worthy of note that the increased prevalence of venereal urethritis in men and of gonorrhea in women, and also the fact that in some areas the clinic incidence of early infectious syphilis is no longer falling, forbids any complacency and underlines the need for vigilance, especially in seaport cities.[12] Here are the main reservoirs of infection, fortunately still half empty, which would rapidly fill in the event of a national emergency. The tracing of contacts, with all its difficulties and disappointments, is now without doubt the most important single measure in the control of the spread of infection. An additional point of interest is obtained from a short comparison of statistics for early and for late syphilis

* References 7 and 8.

in Britain and the United States.[13] This indicates that, in both nations, early syphilis is steadily declining in incidence, while late syphilis is not.

In line with our personal feelings that syphilis is not an unimportant disease because of the recent decline in its incidence, *The Journal of the American Medical Association* [14] makes extensive editorial comment on treatment of syphilis. The opinions expressed are abstracted from a detailed report on the treatment of syphilis presented in a symposium issued by the World Health Organization.[15] Several of the conclusions are worthy of repetition here. Side-reactions to penicillin occur in about 3% of the patients so treated but are rarely severe enough to require discontinuance of treatment and are not as common or as severe as those observed in patients treated with metals. Although treponemes may develop a resistance to metals used in therapy, no penicillin-resistant treponemes have been reported. Because less time and fewer injections of penicillin than of metal are required, a larger proportion of penicillin-treated patients complete the recommended course of treatment. Seroresistance after treatment of early syphilis is relatively uncommon; about 95% of patients with seronegative primary syphilis remain seronegative, and 75% to 80% of those with secondary syphilis also become and remain seronegative. Seroresistance after the treatment of late syphilis is, however, common and is not incompatible with cure. Persistent seronegativity over a period of two to five years in a patient with treated late syphilis is considered strongly indicative of cure. Whether the treatment of early syphilis prevents the late manifestations and in pregnant women prevents the transmission of syphilis to the fetus cannot be determined until penicillin has been used in the treatment of this disease for at least 30 years. The clinical and serologic results of treatment depend on the size of the original inoculum, the number of treponemes in the host at a given time, and the duration of the infection. Despite recent advances in the treatment of this disease, it is still potentially dangerous, and prevention remains the treatment of choice.

Perhaps, after all is said, the big problem in today's syphilology is not syphilis but false positive serologic reactions. Everyday practice is full of embarrassing situations involving the verity of the results of the blood tests for this disease. There is no exaggeration in the story of Aleta White (pseudonym),[16] who has written in dramatic fashion the effects, medical and social, resulting from biologically false reactions to the tests for syphilis.

Along with the data on the major problems of incidence, diagnosis, treatment, and control of the treponemal diseases, much has appeared in recent literature on the reactions to penicillin, and the use of new antibiotics. Perhaps, with continued efforts on the part of individual persons and organizations such as the World Health Organization, the treponemal diseases will vanish from the earth. Clark's [17] address on the natural history of syphilis and levels of prevention is a blueprint for future action. In it are discussed the relationships of agent, host, and environmental factors to the natural history of syphilis and its prevention.

Despite the apparent lack of interest in certain quarters in venereal diseases, and syphilis in particular, there is much activity in the matter of new sources of information: new movies (Syphilitic Venereal Diseases)[18]; new books: Nabarro on congenital syphilis [19] and Welch's "Principles and Practice of Antibiotic Therapy" (with discussion of treponemal and spirochetal diseases by C. R. Rein),[20] and comprehensive compilations by Willcox,† Wortmann,[23] and Tilley.[24] This last-mentioned review is the resumption, after a five-year lapse, of the annual review of syphilis in the *New England Journal of Medicine*. Barnouw's pamphlet was mentioned above. The publications of the World Health Organization of course continue to report the comprehensive surveys and efforts of special commissions throughout the world.

† References 21 and 22.

HISTORY OF SYPHILIS

This review period marks the anniversaries of several milestones in syphilology. Foremost among them is the previously mentioned 10th anniversary of the introduction of penicillin into syphilotherapy. Ehrlich's centennial, which was noted in the last review, was commemorated by additional publications. The Section of Biology of The New York Academy of Sciences, March 13, 1954,[25] presented a glorious tribute to the man who as part of his many-faceted career gave us arsphenamine (Salvarsan, or Compound 606) and who is the father of chemotherapy. Pinkus,[26] too, has written a very glowing tribute to Paul Ehrlich. Within the short span of his 61 years Ehrlich discovered mast cells; formulated arsphenamine; devised specific differential stains for white blood cells and founded modern hematology, discovered a staining method based on acid-fastness; made innumerable contributions to immunology, and did early experimental work with cancer. "The central idea of experimental chemotherapy, and the initial impulse to its triumphant march forward came from Paul Ehrlich."

Fiftieth Anniversary of the Discovery of Treponema Pallidum. — March 3, 1955, marked the 50th anniversary of the discovery of T. pallidum (Spirochaeta pallida). To honor this occasion, Hollander[27] wrote an interesting historical review of the discovery T. pallidum and of the men who devoted their lives to this work. Since Fritz Schaudinn played the major role in this production, his work is especially detailed.

Albert Neisser.—On the centenary of the birth of the "Father of Gonorrhea," Albert Neisser, a review of his life and work was produced by Richter.[28] Although his name is best remembered in connection with gonorrhea, Neisser was no less interested in tuberculosis, leprosy, and, later, syphilis. The transmission of syphilis to monkeys, perfected by Metchnikoff and Roux, enabled Neisser to conduct extensive research, for which he traveled to Java. The many and valuable results were published in 1911 as "Beitrage zur Pathologie and Therapie der Syphilis." Already in 1883 Neisser had described leucoderma syphiliticum. In 1906 his discussions with August Von Wassermann led to the famous Wassermann-Neisser-Bruck serum-complement reaction. With his friend Paul Ehrlich he collaborated on the early experiments which culminated in Ehrlich's discovery of arsphenamine, which Neisser warmly recommended and defended, although opposing complete abandonment of the mercury treatment.

Neisser was continuously concerned not only with therapy but with prophylaxis. He was one of the first to realize that in order to fight venereal disease it was essential to explore and to remove the social causes of prostitution. He spoke strongly in favor of making the health supervision of prostitutes and other diseased persons the concern of City health authorities rather than that of the police and the courts.

Pre-Columbian Osseous Syphilis. — Cole and co-workers[29] make an interesting and well-illustrated contribution to the controversy which still wages as to the pre-Columbian or post-Columbian origin of syphilis in America. They approach the subject through studies made on comparatively recently excavated skeletons or parts of skeletons, 57 in number, from Kinishba and from Vandal Cave in Arizona. These specimens, of pre-Columbian age, were examined for evidence of syphilis. In the tibia of one, changes indicative of diffuse gummatous osteoperiostitis were observed. There was also involvement of the skull. In the tibia of another, the changes were those of classical saber-shin deformity of congenital syphilis. In both of these skeletal remains the lesions were regarded as pathognomonic of syphilis. This is not the first time that syphilis has been noted in pre-Columbian bones. It does, however, add to the evidence.

Harrison,[30] in a philosophical retrospective survey, points out the lessons learned by him during a half century of venereology and adds sound advice for tackling the problems of the future.

T. PALLIDUM AND OTHER TREPONEMES

The Nichols strain of T. pallidum may retain its virulence for as long as 40 years. Durel and Sausse [31] report two cases of syphilis accidentally acquired through handling the Nichols strain after 40 years of cultivation in rabbits.

Lejman,[32] employing staining techniques as well as dark-field and phase-contrast microscopy, studied the morphological changes of T. pallidum under the influence of penicillin treatment in cases of recent syphilis in man. On the basis of his observations he described involutional changes of T. pallidum and the phenomenon of phagocytosis by polynuclear neutrophiles at the time of increasing Jarisch-Herxheimer reaction. It will be recalled that Morton and Ford [33] had noted elongation of treponemes under the influence of penicillin.

Staining of Treponemes. — Beamer and Firminger [34] have detailed a simple modification of Dieterle's method for staining (silver impregnation) leptospira and treponemes in paraffin sections. The results are clear; the organisms are stained a deep brown or black, and the surrounding tissue forms a light golden background. The organisms, though slightly swollen, are plainly visible and retain their characteristic shape with only slight distortion.

EXPERIMENTAL SYPHILIS

There has been continued study of the factors affecting the development of experimental syphilis. These factors include amino acids, temperature, and cortisone. The value of antibiotics, locally applied, as a prophylaxis for experimental syphilis has also been investigated.

Free Amino Acids and Glutathione of Normal and Syphilitic Rabbit Testes.—A comparative study of the biochemistry of tissues was made by Tauber [35] in the hope that comparisons between nonsusceptible and susceptible tissues and between infected and noninfected susceptible tissues might suggest factors necessary for the growth of the organisms. It was found that during the most virulent stage of infection (8 to 13 days) there was a significant decrease in the free glutamine content of testes. Reduced glutathione was found to be distinctly decreased in syphilitic testes.

Role of Temperature in Experimental Treponemal Infection.—In a detailed study, Hollander and Turner [36] have evaluated the role of temperature in experimental treponemal infections. They found that rabbits inoculated multiply intracutaneously on the clipped back with T. pallidum and maintained in a cool room (18 to 21 C) developed lesions at all inoculated sites, whereas animals maintained at a natural summer temperature of 27 to 35 C developed lesions in many cases at only a few of the inoculated sites. Incubation period of rabbits maintained in the cool room ranged from 16 to 20 days; in rabbits maintained in the hot room, from 21 to 72 days. Similar findings were noted in a converse experiment carried out in the winter with some rabbits maintained in a warm room at 29 to 31 C.

In a similar experiment on hamsters, 44 of 45 hamsters in the cool room became infected and 22 of them developed skin lesions, while only 34 of 47 in the warm room were infected, and only 9 developed skin lesions. However, when the animals in the cool room hibernated the lesions regressed.

Left cervical sympathectomy was performed on a group of rabbits in order to effect local changes in temperature, prior to intracutaneous inoculation on the ears. Interestingly enough, none of the cold, unsympathectomized ears developed lesions, whereas lesions appeared on all operated on, warm ears. Since it has been shown that the normal temperature of the outer surface of the ear is approximately 35 C, it would appear that the temperature of the normal rabbit ear is too cold for optimal development of syphilitic lesions.

In the most dramatic experiment carried out, rabbits shaved in various areas were inoculated intravenously with T. pallidum. Multiple lesions appeared confined solely or chiefly to the shaved areas. The shaving was equally effective at the time of or two

weeks prior to inoculation. It was therefore concluded that the lowered temperature of the skin, rather than the trauma of shaving, was responsible for the localization of lesions. The fact that testicular lesions appeared in all animals regardless of whether they were kept warm or cool is interpreted as evidence of the stability of the temperature of the testis, which is therefore a suitable site for the multiplication of treponemes, even in a warm environment.

The authors state that the optimum temperature for multiplication of treponemes in vivo is 35 to 37 C. The need of the treponeme for a relatively cool environment suggests to the authors that the usual delimitation of syphilitic aortitis to the thoracic aorta, in contrast to the abdominal aorta, may be due to a lower intrathoracic temperature, resulting from the inspiration of cool air. They conclude that environmental temperature has an important influence on the course of experimental treponemal infection and that this influence is exerted through its effect on the local temperature of various tissues. They suggest that these temperature phenomena may likewise play a role in the clinical picture of the treponematoses in man.

Mechanism of Action of Cortisone in Experimental Syphilis.—Turner and Hollander [37] also reported upon an extensive and detailed study of the effects of cortisone upon syphilitic rabbits. In contrast to the indurated dusky red flat sharply circumscribed nodules seen in control animals, cortisone-treated rabbits show globoid pale soft spongy lesions. Within a few days after cessation of cortisone treatment lesions increase to enormous proportions, become tense and erythematous, and show new infiltration spreading out from the base of the lesions. This is designated the "rebound" phenomenon. Cortisone causes a marked decrease in cellularity and an increase in mucoid material, which has been identified as hyaluronic acid. Penicillin appears to be equally effective in killing treponemes in cortisone-treated and in control animals. No significant effect was found on serologic test for syphilis (STS) or treponemal immobilization test (TPI) titers, but the white blood cell count was decreased and lymph nodes were found to be smaller in the cortisone-treated rabbits. Wound healing was interfered with. The authors advance a hypothesis that the most striking effect of cortisone therapy is less dependent upon inhibition of antibody formation than upon a direct effect upon the tissues at the point of contact between the parasite and the host, so that the removal of treponemal hyaluronic acid is inhibited. A prominent feature of this effect is alteration of the ratio of hyaluronic acid to chondroitin sulfate. This stimulating paper is of interest not only to syphilologists but also to those concerned with the effects of steroids on the host-parasite relationship.

Antibiotics in Prophylaxis of Experimental Syphilis.—At the meeting of the Subcommittee on Venereal Diseases, National Research Council, held in Washington, D. C., in May, 1952, it was the consensus that it would be advisable to test the potential value of the newer topical antibiotic preparations for their effect in preventing syphilitic infection. Aavik [38] reported on the results of such a study carried out on rabbits in which he tested ointments containing oxytetracycline (Terramycin), chlortetracycline (Aureomycin), erythromycin, penicillin, neomycin, bacitracin, and hexachlorophene soap. With the exception of penicillin ointment, no satisfactory protecting effect was evident with the tested preparations. It should be emphasized, however, that the test conditions were rather severe, which seems to us to be appropriate for an orientation study. With the method described, the control group yielded clinically typical chancres in 96% of the cases. The apparently satisfactory results with penicillin require comment. The absence of a clinically visible lesion does not exclude the possible occurrence of a silent infection, which possibility was not pursued further by lymph node transfer method for two reasons: firstly, local prophylaxis with penicillin ointment seems inadvisable because of the potential danger of eczematous sensitization of the skin with locally applied

penicillin; secondly, it would be extremely difficult, if not impossible, to separate local prophylactic action from the systemic effect of penicillin which may be absorbed into the general circulation from the site of application.

PROGNOSIS

Clinical information, collected at periodic examinations by Peters and co-workers ‡ during 20 years of study of 408 syphilitic patients and 192 nonsyphilitic patients, has furnished evidence that morbidity in the group of untreated male Negroes exceeds that in the nonsyphilitic group and that abnormal roentgen-ray and fluoroscopic measurements of the heart and aorta occur more frequently in the adult male Negro with untreated syphilis. The life expectancy of the Negro man of age 25 to 50 years with untreated syphilis is reduced by about 17%. The lesions characteristic of syphilitic involvements in the Negro male are to be found for the most part in the cardiovascular system. It is estimated that a Negro male with syphilis of more than 10 years' duration for which he has received no treatment and with sustained seropositivity prior to death would have, roughly, a 50-50 chance of demonstrating syphilitic cardiovascular involvement at autopsy. In the respiratory, digestive, hemopoietic, endocrine, urinary, and reproductive systems, the incidence of abnormalities among syphilitic patients was not significantly different from that among the control patients. In 30.4% of the syphilitic patients examined at autopsy, syphilitic involvement of the cardiovascular or the central nervous system was established as the primary cause of death. The distribution of the causes of death among the syphilitic patients, aside from syphilis itself, was not different from that in the nonsyphilitic group. Although much progress has taken place in the Macon County study, the economic standing and cultural isolation of most of those in this study have not changed remarkably. Previous medical reports on this group of Negroes inferred that the socioeconomic and health factors were so uniform in Macon County that mortality or morbidity rate difference between the control and syphilitic groups could be attributed solely to syphilis. Olansky and his group [41] sought to determine whether nonsyphilitic subjects had any advantages, other than freedom from syphilis, which would predispose them to longer healthier lives. In no instance could statistical significance be demonstrated in the measures of social status of the two study groups. Data presented from this study have shown that the socioeconomic differences between persons having syphilis and persons who do not are slight.

‡ References 39 and 40.

DIAGNOSIS OF SYPHILIS

Advances in diagnosis of syphilis come in spurts. There has been but little new in this review period beyond consolidation of certain aspects of serodiagnosis and the treponemal immobilization test. Du Pasquier [42] describes in detail all forms of skin tests ever proposed for the diagnosis of syphilis. He divides his subject matter into tests based on (1) antigen extracts of viscera of the fetus infected with hereditary syphilis; (2) cultured antigens; (3) antigens derived from animal organs, in particular the rabbit syphiloma, and (4) antigens made of suspensions of treponemes.

Serodiagnosis

Recent advances in serodiagnosis have been reviewed by several authorities.§ These studies indicate the important trends: standardization, the use of cardiolipin antigen and other antigens (sitolipin and spirochetal),‖ more use of the slide and filter paper methods,¶ the performance of more quantitative procedures, and a number of technical factors influencing the outcome of the tests.#

Biologic False Reactions

A most active field investigation in serodiagnosis is that of biologically false reactions to the tests for syphilis. This problem has in

§ References 43-48.
‖ References 49-61.
¶ References 62-66.
# References 67-77.

fact become greater in a sense than syphilis itself. It has not been solved; actually it has become more acute, as a result of the treponemal immobilization and other tests.[78] General discussions of this problem * and reference to its occurrence in "normal" persons [83] in specific diseases, pregnancy,[84] lymphogranuloma venereum,[85] leprosy,† systemic lupus erythematosus,‡ and virus pneumonia [91] have appeared. The presentation of Moore and Lutz [82] is a useful summary of the present situation. They state that the margin of error in recognition of the biologic false positive (BFP) phenomenon by means of the TPI test is 2% or less. The chronic BFP phenomenon has been observed predominantly in females (70%). The chronic BFP reaction is more frequent in younger persons. Clinical disease usually does develop in many chronic BFP reactors, and the phenomenon is far from innocuous. Indeed, the physician is no longer justified, when he has identified a chronic BFP reactor, in dismissing his patient with congratulations on the absence of syphilis. Instead, he is faced with a lengthy and detailed clinical investigation to identify the cause of the BFP reaction. The chronic BFP phenomenon is one manifestation of tissue injury, probably chiefly of collagen and vascular tissue. The first manifestation of tissue injury to appear is perhaps the BFP phenomenon itself, together with or shortly followed by an increase in sedimentation rate and thymol turbidity; still later, by strongly positive cephalin flocculation tests and quantitative increase in serum globulin, and much later still, perhaps not until after several or even many years, by a disturbed electrophoretic pattern and the appearance of L. E. cells. The L. E. cell phenomenon seems to be a late development, appearing only after some years of episodic illness. Dysgammaglobulinemia may be responsible for the BFP reaction itself, increased sedimentation rate, abnormalities of protein flocculation tests, quantitative increase in serum globulin, alteration in electrophoretic pattern of the serum, and development of the L. E. cell phenomenon. The chronic BFP phenomenon has a more serious immediate (within the first few years of its discovery) prognostic import for females than for males. Actually or potentially alarming signs of illness of any form have appeared in only 31.8% of the males with chronic BFP reactions and in 51% of the females. The BFP phenomenon, acute or chronic, is frequent. The exact frequency depends on the population group under investigation. In white patients of upper educational and socioeconomic level, it appears to approximate 40% among routinely discovered seropositive STS reactors. In an outpatient clinic population of lower educational and socioeconomic level, approximately 90% Negro, only about 10% of clinically and serologically comparable patients are BFP reactors.

Treponemal Immobilization Test

In spite of continued and anticipated progress in the development of new specific methods for the definitive diagnosis of syphilis,[92] the treponemal immobilization test still holds the forefront. Many new technical "wrinkles" have been proposed (preservation of organisms by freezing,§ improvement in preservation medium,‖ and the use of streptomycin to combat contamination of T. pallidum suspensions.¶ In spite of the simplification, improvement, and performance on a larger scale, it is obvious that the treponemal immobilization test cannot replace but may supplement the currently available serologic procedures. Objections to the test on the basis of cost [99] are no longer tenable, as Canadian experience [100] indicates that the average cost for the performance of a single TPI test is less than $4.00. Ledbetter,[101] who found the procedure practical on a service-wide basis in the U. S. Navy, estimated that the cost of a TPI test has now been reduced to $7.50. A survey of the reports on comparative study of this test in

* References 79-82.
† References 86-87.
‡ References 88-90.
§ References 93 and 94.
‖ References 95 and 96.
¶ References 97 and 98.

various phases of syphilis with the current blood tests indicates a continuing favorable trend.# While MacPherson, Ledbetter, and Martens [115] rate this procedure from the specificity standpoint as "the best available test for either establishing a definite diagnosis or ruling out the presence of syphilis," Boak, Miller, and Carpenter [102] wisely point out that, as is the case with all tests, reproducibility of results in the TPI test depends primarily on the laboratory. Wilkinson's [116] summary of the field of use of the TPI test is a valuable statement for the practitioner. In early (primary and secondary) syphilis it offers no advantages over existing diagnostic methods. In late (symptomatic) syphilis where the STS is positive, the TPI test may be expected to be positive; in these circumstances the test has only confirmatory value and is not indicated for routine use. In the diagnosis of suspected latent syphilis it is a most valuable confirmatory test. In such cases, if the TPI test is negative and this finding is confirmed by examination of a second specimen of serum, the positive STS should be strongly suspected of being nonspecific in nature. In patients who present signs or symptoms which may be attributable to late syphilis but in whom the STS is negative, a positive TPI test is strong confirmatory evidence of the disease. A negative TPI test does not absolutely exclude syphilis, but it renders the diagnosis improbable. Although the immobilization test is highly specific, it does not distinguish between syphilis and the other treponematoses. In the routine serology of syphilis it does not replace the STS but should be used as an ancillary to it.

Cerebrospinal Fluid

Spinal Puncture Headache.—Eversole and Rokowski,[117] of the Lahey Clinic, Boston, report that the usual cause of postlumbar puncture headache is the reduction of cerebrospinal pressure when spinal fluid leaks through the hole made in the dura by a spinal puncture needle. A greater differential between the cerebrospinal fluid pressure and the intracranial venous pressure is produced, bringing about dilatation of the venous structures and some increase in brain volume because of venous dilation and edema. The headache may occur in a few hours or after several days and may be slight but is frequently deep and dull. Pain may be referred to any cranial region but is usually frontal. The ache is intensified by shaking the head or by jugular compression or when the patient is standing. Patients overly sensitive to pain or with previous severe headache should not be given spinal anesthesia. When necessary, single injection of spinal anesthesia should be used, but not the continuous method. Headache occurs less often when a special needle, resembling the point of a pencil, is used or if the ordinary spinal needle is held with the bevel parallel to the long axis of the body. Injection of 10 to 20 cc. of isotonic saline solution into the epidural space immediately after anesthesia may prevent headache. Spinal puncture headaches are usually relieved by placing the patient in a horizontal position and by injecting isotonic saline into the subarachnoid or epidural space. Intravenous injection of hypotonic solution may be of benefit, but hypertonic solutions should not be used.

Cerebrospinal Fluid Protein.—Flodén [118] made an extensive investigation of whether there was a method for determination of protein in the cerebrospinal fluid which allowed for accurate and reproducable results. He also attempted to analyze cerebrospinal fluid protein conditions in syphilis with such a method to find out the protein "pattern" in various phases of syphilis and its value in determining activity of the neurosyphilitic process. The Izikowitz method was found to permit reliable protein estimation in the cerebrospinal fluid. Protein conditions in syphilis material were found to exhibit certain characteristics, constituting what might be termed protein "patterns." Changes in the protein conditions provide a good conception of the so-called neurosyphilitic process. The protein changes alone cannot

#References 102-115.

be used for differential diagnosis between types of neurosyphilis as the specific course in the individual case. Nor can the protein changes alone be used for differential diagnosis between syphilis and other diseases. Protein changes may occur in other diseases as well.

Spinal Fluid Findings Among Syphilitic and Nonsyphilitic Persons.—Cutler and his co-workers [119] have also contributed significantly to our knowledge of normal variations in spinal fluid cell counts and total protein determinations. Spinal fluid examinations were performed on hundreds of nonsyphilitic patients and on hundreds of patients with untreated primary and secondary syphilis. Cell counts and protein determinations in nonsyphilitics, in primary and secondary syphilitics with negative spinal fluid serologic tests for syphilis, and in patients with primary and secondary syphilis with positive spinal fluid serologic tests for syphilis were compared. The findings were startling. No significant difference was found in the cell counts and protein determinations between nonsyphilitics and syphilitics with negative spinal fluid STS, and the percentage distribution of total protein was approximately the same in these two groups. Syphilitic patients with positive spinal fluid STS tended to have higher cell counts and protein determinations than did the patients in the other groups, but the differences were less striking than would be anticipated. Abnormalities in both cell count and total protein content were found to be of greater diagnostic import. Forty per cent of the syphilitic patients with positive spinal fluid STS had more than four cells and over 40 mg. of protein, while less than 2% of the other group showed this increase in both cells and protein. This paper should sound the death knell of the classification of spinal fluid abnormalities into Groups I, II, and III. Group I fluids (which show increase in cells and/or protein with a negative spinal fluid STS) are, in our opinion, clearly demonstrated by this study to be of no pathologic significance.

CLINICAL MANIFESTATIONS

New and reevaluated old facts about the clinical aspects of syphilis continue to appear in the literature. Lucas,[120] on the basis of his experience with it, indicated that lymph node aspiration biopsy might be useful as a screening procedure. Kardel-Vegas and associates [121] reported a case of keratoderma punctatum syphiliticum. Rajam and Rangiah [122] presented three cases of early syphilitic hepatitis, of which two patients had early acquired syphilis and one had congenital infection. They recommended routine liver biopsy to determine the extent and incidence of liver involvement in syphilis. Bradford [123] also reported a case of pulmonary syphilis with the diagnosis made before death. This was the first case to be localized bronchographically and the first to be treated by pneumonectomy. An example of syphiloma of the pancreas, followed for 14 years after treatment, was reported by Castigliano.[124] The problem of syphilis and malignant disease has received attention. With his well-known thoroughness and statistical precision, Rosahn [125] has studied the frequency and distribution of malignant disease, as determined at autopsy, in a group of syphilitic white persons over 20 years of age. A control group of nonsyphilitic persons was similarly studied. He found that malignant disease in general occurred no more frequently among syphilitics than among the nonsyphilitic controls. However, there was suggestive but not conclusive evidence that syphilitic persons with malignant disease have primary lesions located on the tongue more frequently than do nonsyphilitic persons with cancer.

Late Syphilis—Paroxysmal Cold Hemoglobinuria.—Jordan and Schlesinger [126] present a short history of paroxysmal hemoglobinuria and briefly differentiate between syphilitic paroxysmal cold hemoglobinuria and nonsyphilitic paroxysmal cold hemoglobinuria. In an extensive study of one patient with syphilitic paroxysmal cold hemoglobinuria, Jordan comes to the conclusion that the red cells show an abnormal tendency to

destruction by the hemolysin. His experiments suggest that there exists not only a serious abnormality (presence of the biphasic hemolysin) but also a defect of the red cell population. Jordan was not able to define the possible abnormality in the paroxysmal cold hemoglobinuria red cells more clearly. It is suggested that as a consequence of syphilitic infection some (not yet defined) lesion of the red cells occurs. The damaged red cell acts as an antigen, which process results in the formation of an autoantibody directed against this red cell. This antibody would then be the hemolysin, which was first described by Donath and Landsteiner.

Factors Leading to Development of Late Manifestations of Syphilis.—Utilizing a corps of Public Health Service special investigators, Thomas [127] has carried out a detailed study of the various breakdowns in control measures which, by permitting syphilitics to remain undiagnosed or untreated, lead to the development of late manifestations of syphilis. During the period Jan. 1, 1944, to Dec. 31, 1949, six hundred eighty-seven patients with a diagnosis of late active syphilis were admitted to the Bellevue Hospital syphilis service. The special investigators spent two years collecting data concerning the previous medical history of these patients which would throw light on the reason why they failed to receive treatment which might have prevented progression. A card was prepared for each patient giving a list of all clinics, hospitals, and physicians by whom the patient had been observed. It was found that many private physicians keep either no records or inadequate records of medical care given to patients, that many clinics and hospitals destroy records after a few years, and that many records do not include pertinent findings. In some hospitals each admission was kept as a separate entity, which militated against completeness of records. The study highlights the need for a consolidated easily read patient record for intelligent management of chronic disease. Eighty per cent of the Negro males and eighty-nine per cent of the Negro females studied had not been born in New York City. Fifty-seven per cent of white males and forty-three per cent of white females had not been born in New York City, most of these being immigrants. Syphilis was first diagnosed at Bellevue Hospital in 22.4% of the patients. An additional 13% diagnosed previous to admission to this study had already developed late manifestations before syphilis was detected. Thus, in 35.5% the disease had progressed to the symptomatic stage before infection was discovered. In this group of patients spinal fluid examination had been utilized as a diagnostic aid to only a small extent. Spinal fluid examinations were performed for the most part to confirm clinical findings suggestive of neurosyphilis rather than as a routine measure to detect neurosyphilis in the asymptomatic stage at a time when late crippling forms might be prevented by adequate treatment. It was found that 174 of the 509 patients whose syphilis was first diagnosed in the late stage had had some medical care between the date of syphilitic infection and the date of its detection. The patients' histories indicated that there were 344 missed opportunities for detection of infection. Hospital wards were most remiss in this respect. In some cases, no STS was done; in others, positive STS reports on the record were ignored. Many case-holding failures occurred (64% of the patients) and were evenly divided among private physicians, hospitals, and clinics. Most of the patients were under some type of medical observation for more than a year between the time of detection of syphilis and admission of this study. The authors point out that the patient's share of responsibility lies principally in his failure to seek diagnosis and treatment in the early stages of syphilis, as well as in lack of cooperation after diagnosis has been made, through disregard of the physician's instructions, carelessness, lack of realization of the need for treatment, or lack of acceptance of treatment. The physician has the implied responsibility of being able to handle with current standards of professional competence any patient whom he accepts for care. He must instruct the patient regarding his disease and its management. In hospital, clinic, and private phy-

sician records, date of therapy and dosages of drugs were frequently not recorded; no effort was made to diagnose the stage or type of disease, and on hospital records the report of a positive STS on blood taken when the patient was admitted often did not reach the chart until the patient was discharged, and no follow-up was instituted. In other patients no report of the STS was found on the record in spite of notes that blood was drawn for routine tests. Illegible handwriting and esoteric abbreviations often rendered the record valueless. A review of hospital records revealed that frequently the hospital physician made no effort to familiarize himself with the history of previous admissions to the same hospital. It is the responsibility of public health officials to promote proper patient education and to carry out the best possible case-finding and case-holding procedures. This interesting study should point out to members of the medical profession wherein they have failed in permitting syphilis to progress undiagnosed or untreated to active late disease, despite multiple opportunities to diagnose and treat.

CARDIOVASCULAR SYPHILIS

The clinical manifestations of cardiovascular syphilis have been given much attention. Like other phases of syphilis there is a downward trend in this manifestation of the disease (Whiteman and Mihaly [128]). The general discussion by Katz and Scott [129] gives a coordinated review of the subject. The use of the aortic electrokymogram in normal subjects and in patients with aortic insufficiency has been discussed by Brandfonbrenner and Eisenberg.[130] Aortic aneurysms have been discussed from a variety of viewpoints. Syphilis is perhaps assuming a lessened role in the causation of these lesions (Blakemore [131]).

Aortic Aneurysms.—Cranley, Herrmann, and Preuninger [132] reviewed the autopsy protocols and clinical records of all patients at the Cincinnati General Hospital with a pathologic diagnosis of aneurysm of the aorta, between the years 1926 and 1952, inclusive. There were 103 dissecting aneurysms; these were excluded from the study. A saccular or fusiform aneurysm was found in 243 subjects out of 17,168 autopsies. This is an incidence of 1.4%. Forty-five per cent of the aneurysms were the direct cause of death, and an additional 10% were most probably the cause of death. Eighty-two per cent of all aneurysms were due to syphilis, and 14% to arteriosclerosis. The incidence of syphilitic aneurysms has declined rapidly since 1940, only 2 being found in 1395 autopsies during the years 1951 and 1952. Sixty-one per cent of the syphilitic aneurysms proved to be certainly or most probably fatal at an average age of 51 years for white patients and 43 years for Negro patients. Twenty per cent of the patients with a syphilitic aneurysm and twenty-seven per cent of those with an arteriosclerotic aneurysm were found to have multiple aneurysms. The roentgenogram provided the most accurate means of establishing the diagnosis of aortic aneurysms.

The syphilitic aneurysms were located in the thoracic aorta in 89% of the cases and in the abdominal aorta in 11%. The mechanism of death in fatal aneurysms due to syphilis was rupture in 53 cases (59%) and compression and erosion of vital structures in 37 cases (39%). In addition, there was one postoperative death.

The duration of life from onset of symptoms to death in the syphilitic aortic aneurysm group varied from less than a day to 25 years in one instance. Fifty-nine per cent of the patients died within one year of the onset of symptoms, and seventy-seven per cent died within two years of the initial symptoms.

Roentgenologic Diagnosis of Aneurysm of the Thoracic Aorta.—Aneurysms of the thoracic aorta, most commonly of syphilitic origin, occur most frequently in the ascending aorta and may be either saccular or fusiform. The diagnosis depends upon demonstration of a bulge in the aorta, and this is, roentgenographically, often a difficult problem. Roentgen techniques in differential diagnosis of aortic aneurysm, syphilitic and nonsyphili-

tic, are described by Levine and his colleagues.[133] They favor the right posterior oblique position. By the use of the techniques they described, the need for the more elaborate angiocardiography is obviated.

Dissecting Aneurysm of the Aorta.—Dissecting aneurysm of the aorta has frequently been mistaken for syphilitic aortic disease. After a description of the principal clinical features of dissecting aneurysm and a review of the beliefs held on its pathogenesis and mechanism, the differential diagnosis from syphilis, both antemortem and postmortem, is discussed by Horne.[134] Three case histories (one with postmortem report) illustrate the difficulties encountered in differential diagnosis. It is pointed out that if the current decline in the incidence of syphilis continues there is likely to be a relative increase in the incidence of dissecting aneurysm.

Syphilitic Aneurysm of the Left Ventricle of the Heart.—Brink and Barnard[135] described a case in a Bantu man in which a calcified cystic mass situated in the base of the left ventricle was shown to be a cardiac aneurysm due to syphilis. Although the lesion was eventually found to involve the whole thickness of the myocardium, the electrocardiographic findings were not those of a through-and-through infarct nor those of an aneurysm. Heavy mural calcification of the cardiac aneurysm led to the mistaken diagnosis of a hydated cyst and to a thoracotomy. Sections from this aneurysm showed actual ossification and suggested strongly that its cause was gummatous myocarditis.

NEUROSYPHILIS

The differential diagnostic importance of neurosyphilis is indicated by the reports of bizarre types of neurosyphilis (syphilitic gummatous meningitis involving the Gasserian ganglion,[136] Charcot's joint in diabetes mellitus,[137] depressive reaction masking neurosyphilis,[138] nervous system manifestations of pulseless disease,[139] acute meningovascular syphilis during the poliomyelitis season,[140] and general paresis and multiple sclerosis[141]). Rao[142] has seen 31 cases of neurosyphilis in Hyderabad. There were no instances of general paresis or tabes in this series. The main types were spinal syphilis and cerebral syphilis.

Paresis death rates have been divided by Donohue and Remein[143] into three periods: 1900 to 1923, a period of practically no preventive effort to control syphilis; 1923 to 1938, a period of little preventive control, but one in which malaria and other forms of fever therapy were used, and in 1938 to 1951, the period of a national syphilis control program. Fever therapy was successful in reducing mortality, but the incidence did not diminish. By 1938 mortality from paresis had reached a plateau and no further reduction seemed likely through fever therapy. About four years after inception of the national syphilis control program, there were reductions in deaths from paresis. The summation of years of life lost by deceased paretic patients in 1948 amounted to 63,057 years. An estimated 34,713 productive years of life were lost because of premature deaths from paresis in the same year. A saving of 38,113 years of life expectancy resulted from the reduction of mortality between 1937 and 1948. The value of total earnings lost to persons who died from paresis in 1948 amounted to $45,714,160, compared with $95,127,717 which would have been lost under precontrol mortality conditions. A savings of $49,413,557 in earnings may be attributed to the control program. As far as individual states are concerned, in Arizona,[144] for example, there are more than 100 persons in the State mental hospital committed as a result of paresis. These patients are costing the taxpayers over $100,000 a year. In Idaho,[145] 34 patients found to have neurosyphilis would have cost the State of Idaho, at $1800 per year for care of each mental patient, $61,200 per year, eventually. The average stay for such patients is 10 years, and so spending the $25,000 for case-finding and treatment saved the state $612,000.

OCULAR SYPHILIS

As mentioned for neurosyphilis, syphilis of the eye is also often difficult to differentiate from similar changes produced by other diseases. In congenital syphilis, therefore, favorable comment on the use of the slit lamp is welcome. For example, Dunlop and Zwink [146] used the slit-lamp microscope in the investigation of ocular disease in 117 certain cases of congenital syphilis. They found the incidence of interstitial keratitis in cases of congenital syphilis in clinic practice to be 63%. This incidence was reduced to 44% by excluding all those who presented themselves at the clinic because of interstitial keratitis. Thus, the real incidence in clinical practice lies between 44% and 63%.

Although the Argyll Robertson pupil has been confused with Adie's syndrome, it is usually thought of as being due to syphilis. Kissel, Arnould, Hartemann, and Dureux [147] reported an example of a unilateral Argyll Robertson pupil in the course of a case of pernicious anemia. Naquin [148] also observed Argyll Robertson pupils following herpes zoster ophthalmicus.

Unilateral Argyll Robertson Pupil.—Apter [149] found 13 cases of unilateral Argyll Robertson pupil among 46 cases of neurosyphilis. She employed the same criteria for diagnosis as were described by Argyll Robertson in 1869: (1) The pupil is small; (2) the pupil does not respond to light no matter how bright; (3) the pupil has a brisk response to convergence - accommodation; (4) the pupil dilates imperfectly in response to atropine; (5) the retina is sensitive to light. The slit lamp biomicroscope was used in this study and was shown to provide a very sensitive accurate technique. Gross abnormalities of the iris, such as transillumination, absence of collarette, and fine radial striations were associated with each miotic light-rigid pupil. Cocaine produced dilatation of most of these miotic pupils, and after this mydriasis the pupils were capable of constricting when light was incident on the ipsilateral or contralateral retina.

The findings in this study are incompatible with the theory of a central nervous system pathogenesis of the Argyll Robertson pupil. None of the central nervous system lesions proposed thus far can explain a unilateral miotic light-rigid pupil. Those who support a theory of a central nervous system pathogenesis of the Argyll Robertson pupil are forced to postulate two lesions—one to explain the miosis and another to explain the light rigidity. Since each sign—the miosis and the light rigidity—may occur separately in many diseases, while the combination of miosis and light rigidity occurs only in syphilis, it would appear worth while to search for a single lesion to explain the Argyll Robertson syndrome. The manner in which the present clinical data support the postulate that the single lesion may be in the iris itself was the subject of another report by Apter.[150]

CONGENITAL SYPHILIS

Selective Filtration of Syphilitic Reagins Through the Placenta.—Three serologic tests for syphilis, the Bordet-Wassermann reaction, the precipitation reaction of Wadsworth and Brown, and the clarification reaction of Meinicke, were performed by Vogt [151] on serums from 107 newborn infants, and the results were compared with the same tests on serums from the mothers taken prior to delivery. The mothers were seropositive during the late stages of the pregnancy. Meinicke's clarification reaction was negative in the serums from all 107 infants, even when the serum reagin titer of the mother was high at the time of delivery, and the other tests were positive in the serum of the infant. The author concluded that the Meinicke reaction is not suitable for the detection of syphilitic reagins in the serums of newborn infants because the reaction is always negative.

Congenital Syphilis: A Follow-Up Study with Reference to Mental Abnormalities.—Hallgren and Hollstrom [152] presented a review of the literature as a preliminary to the study of 500 instances of congenital syphilis seen at the Welander Home, in Stockholm, 1900-1950. Of 500 patients, 117 manifested mental defects. Of the 500, again, 50 have died, only 5 directly from syphilis. The mortality is not above the national average for

the general population. Statistical breakdowns are given of the incidence of mental defects in these children by age, sex, and other criteria. Of 259 observed for three years or more, 36 had neurologic symptoms. Regimens of treatment used through the years are described briefly and range from mercury and bismuth and arsenicals through penicillin. No difference was noted in the incidence of mental deficiency among the patients treated by the different methods. Additional analyses are presented with respect to incidence of mental deficiency by birth weight of the patient, by maternal symptoms, by mental condition of the mother, and by extent of treatment of the mother.

GENERAL THERAPY

As Thomas [153] has stated, the treatment of syphilis is relatively simple. However, there are still certain doubts in the minds of authorities regarding just what is proper therapy. Simons,[154] for example, makes the disheartening remark that, although penicillin therapy of syphilis raised great expectations, a number of therapists have departed from their early enthusiasm and have returned to treatment with neoarsphenamine and bismuth in combination with antibiotics. This is hardly in keeping with our experience. In addition, Sir Alexander Fleming in the January, 1955, issue of *The Practitioner* expressed the reassuring view that there is not going to be a general development of resistant organisms that would render penicillin useless. In the same issue McElligott,[155] advisor on venereal diseases to the British Ministry of Health, states that procaine penicillin in oil with 2% aluminum monostearate (PAM) has so far proved to be the most suitable preparation for the treatment of syphilis in all of its stages. It will be recalled that actually penicillin is useful in patients resistant to arsenicals and bismuth.[156] Idsøe and Guthe [157] in their comprehensive article also believe that PAM at present dominates syphilis therapy. Because in early syphilis the treponemes are in most cases killed after continuous exposure to penicillin for from one to two weeks, the practice of combining penicillin with subcurative doses of arsenicals and bismuth is unwarranted. Kolmer,[158] who has carefully outlined the dosage schedules for all phases of syphilis, still uses potassium iodide orally in addition to the penicillin therapy of latent, tertiary acquired, and late or tardive congenital syphilis. He believes that this combination deserves more attention at this time. Kolmer's system of therapy differs from most schedules in that he states that he would treat "too much" rather than incur the risk of administering too little.

While PAM is widely used, other penicillin products are being employed in the treatment of treponemal diseases. Rein and his co-workers [159] present another report on the use of a combination of three penicillin salts (potassium penicillin G, procaine penicillin G, and benzathine penicillin G). They found higher and more prolonged blood levels resulting from this combination than from PAM in similar dosage. Initial clinical trials in syphilis, yaws, and pinta were highly encouraging, and these authors feel that this type of penicillin preparation should be of special value in those countries where the majority of the patients must be treated with a single injection schedule.

Abortive Treatment of Syphilis.—Kanee and Nelson [160] discussed a widely used plan which they call "the overtreatment method" whereby all patients with gonorrhea are given 1,200,000 units of PAM in order to abort possible concurrently acquired syphilis. In more than 400 patients treated by this method and followed subsequently with serologic tests for a minimum period of six months, not a single syphilitic infection appeared. Following the thought further, the authors advised that patients diagnosed as having chancroid be given 1,200,000 units of PAM and patients with dark-field negative undiagnosed penile lesions be given 2,400,000 units. In addition, when previous treatment has been given for either a urethral discharge or a sore, 2,400,000 units of PAM is given. On the basis of their experience, the authors recommend minimal follow-up of "overtreated" patients with gonorrhea in

order to free epidemiologic field workers from barren case-holding procedures into the more productive field of new case finding. They state that in this concept of overtreatment of one infection to abort or minimize the results of a severer infection there is an outstanding example of the results obtained by the clinical application of the preventive concept in medicine.

TREATMENT OF EARLY SYPHILIS

It is appropriate at this time, 10 years after the introduction of penicillin into syphilotherapy, to report surveys in various parts of the world of current treatment practices in early syphilis. On the basis of a questionnaire submitted to 277 leading university and other major venereal disease clinics in North and South America, Southeast Asia, the Western Pacific area, the Eastern Mediterranean area, and Europe, Willcox and his co-workers [161] present an interesting study of current practices for treatment of early syphilis throughout the world. Sixty-five per cent of the clinics used penicillin alone. All clinics in North America relied on penicillin alone, while 48% of those in Europe gave adjuvant therapy with arsenic, bismuth, or mercury. PAM was the drug of choice in 82% of the schedules studied. It was used in 91% of the clinics in the Americas and Southeast Asia but in only 60% of European clinics. Procaine penicillin G in water and crystalline penicillin G were used in approximately one-fifth of the European clinics. The commonest total dosage was 4,800,000 to 6,000,000 units. However, 39% of the European clinics administered 10,800,000 units or more for secondary syphilis. Fifteen per cent of clinics using PAM gave a large initial dose of 2,400,000 units in secondary syphilis, and 54% used an initial dose of 1,200,000 units or more. Mean duration of the initial penicillin treatment varies from 10 days in the Eastern Mediterranean area to 15 days in Europe. Eighty-three per cent of the clinics used the same schedule of treatment for all stages of early syphilis. Fifty-nine per cent of the clinics gave single or multiple injections with intervals of two to seven days, while 41% gave daily injections of PAM. The authors point out that these findings 10 years after the introduction of penicillin indicate a situation not dissimilar to that following introduction of the arsphenamines, at which time many clinicians were not prepared to abandon mercury in favor of the arsphenamines. Penicillin therapy has taken root more slowly in Europe than in other parts of the world, but acceptance of this antibiotic as the sole agent in the treatment of early syphilis is gradually increasing in all areas.

Willcox,[162] in a review article which briefly discusses the history of the treatment of syphilis from mercury and guaiacum to procaine penicillin with aluminum monostearate and present-day treatment, states that many British clinics at the present time are giving initially an eight-day course of 600,000 units of procaine penicillin with aluminum monostearate daily followed by 10 bi-weekly injections of 900,000 units of penicillin of the same type. Willcox admits that this is probably overtreating, but he says that this is a margin of safety. Further, he states that there is some force to the argument that when given only a few injections patients will take the disease, its implications, and its consequences less seriously; a longer course enables the patient to realize his responsibilities while the clinic is dealing with the question of contacts and the like. A suggested course of therapy for patients with early syphilis is an initial injection of 2,400,000 units of procaine penicillin with aluminum monostearate followed by 600,000 units daily for eight days or 900,000 units two to three times weekly for six injections.

The experience of the Venereal Disease Program of the U. S. Public Health Service in evaluating procaine penicillin G in oil with 2% aluminum monostearate in the treatment of primary and secondary syphilis has been reported by Cutler and coworkers.[163] Their conclusions are as follows: 1. As little as 300,000 units of PAM is effective in the treatment of seronegative primary syphilis. 2. The optimum dosage for seropositive primary syphilis appears to

be 2,400,000 units. 3. In secondary syphilis best results are obtained with the highest dosage employed, 9,600,000 units. 4. No difference in results is observed when PAM is administered in a single session or in divided doses over a period of several days.

TREATMENT OF EARLY SYPHILIS WITH ANTIBIOTICS OTHER THAN PENICILLIN

Carteaud,[164] along with others, contends that penicillin does not represent the only antibiotic active against syphilis. There are others of variable value. Carteaud studied oxytetracycline, but he could not, because of inadequate material, draw definitive conclusions as to its worth.

Carbomycin in Early Syphilis.—Eleven patients with early syphilis reporting to the venereal disease control clinic of the Memphis and Shelby County Health Department were treated with carbomycin by Buckinger and his colleagues[165] to ascertain the extent of the treponemicidal activity of the antibiotic. The results obtained in these 11 patients, observed since July, 1953, were satisfactory. Oral carbomycin in dosages of 2 or 3 gm. daily was effective in bringing about disappearance of treponemes from lesions in about 36 to 72 hours after the initial dose was given.

Treatment of Early Syphilis with Chloramphenicol (Chloromycetin).—On the basis of brief observation of nine patients with dark-field positive early syphilis, Mazzini and Blasi[166] conclude that chloramphenicol is a potent weapon for combating early stages of syphilitic infection. Their conclusions are based upon clinical healing, serologic trend, and reversal of the dark-field examination to negative within 48 hours. The authors recommend a daily dose of 100 mg/kg. body weight for six to eight days. Because of the brief period of observation and the paucity of data presented, we are not overly impressed with the validity of the authors' conclusions.

TREATMENT OF LATE SYPHILIS

Treatment of Late Syphilis in Seamen.—For the treatment of late syphilis in seamen, Willcox[167] recommends 12 to 14 daily injections of 900,000 units of penicillin with aluminum monostearate (PAM). It is stated that a sailor whose syphilis is satisfactorily under control may go to sea; that a patient with cardiovascular involvement must retire to shore, and that those having tabes dorsalis would be dangerous to themselves and their fellows if allowed to go to sea.

TREATMENT OF CARDIOVASCULAR SYPHILIS

The great difficulty in evaluating therapy in cardiovascular syphilis cited by others was supported by Johnson and his coworkers[168] in their evaluation of 19 cases treated five years ago with 4,008,000 units of penicillin. From their study, it appears that the results of penicillin therapy are no better than those of treatment with adequate amounts of heavy metals or arsenic. Although 4,008,000 units of penicillin appeared to be an adequate dose in the majority of living patients, progression of cardiovascular changes occurred in two, Johnson feels that larger doses, perhaps 9,000,000 to 10,000,000 units, might be better. The orthodiagram continues to be an important prognostic procedure. Patients were observed to remain well and active with marked hypertension, wide pulse pressure, and severe electrocardiographic and roentgenographic changes. The prognosis was poor when cardiac symptoms indicated a reclassification of functional capacity. On the other hand, as the result of penicillin therapy administered to 111 patients with cardiovascular syphilis, Edeiken and Beerman[169] found that penicillin is the safest agent yet produced for that purpose. Experience indicated that penicillin could be given to these patients without fear of a severe reaction. From the reaction standpoint, it was unnecessary to prepare patients with bismuth or iodides. The dosage suggested was 9,600,000 units of penicillin given in divided doses over 10 to 14 days. The suggestive evidence that the course of the

disease is favorably influenced by penicillin consisted of change in aortic diastolic murmurs after treatment in some cases, favorable effect upon patients with paroxysmal dyspnea and congestive heart failure, improvement in some patients having angina pectoris, and subjective improvement being experienced by most patients.

Resection of Aneurysms.—DeBakey and co-workers [170] reported on the aortic resection of 150 patients with either aneurysm or occlusive disease. In their initial series there were seven patients with aneuryms of the thoracic aorta treated by resection and replacement with homograft. The lesions were considered syphilitic in origin in four. Of 49 cases of aneurysm of the abdominal aorta, only one was considered to be syphilitic. Of the 31 cases of occlusive disease of the aorta, none was thought to be due to syphilis. No special comment can be made on the few syphilitic cases in comparison with the group as a whole.

Six cases of aortic aneurysm in which operation was done were analyzed by Dubost and Dubost.[171] They found that the most satisfactory progress being made at this time in the treatment of aortic aneurysms is in those of the infrarenal segment. Active surgical therapy is called for in this disease, even though it be merely palliative.

TREATMENT OF NEUROSYPHILIS

Spinal Fluid Evaluation in Neurosyphilis.—Results of penicillin therapy of 86 patients with asymptomatic neurosyphilis are reported by Rausch.[172] Results of spinal fluid examinations made before and at least 15 months after therapy showed that the cell counts presented the highest percentage of improvement, the protein and coloidal gold tests were next, while the complement-fixation test showed a decreasing titer in the lowest proportion. Results of tests must be interpreted as a whole. One item by itself does not give complete information on the central nervous system involvement. Spinal fluid comparisons before and after treatment provide definite measuring devices. Since 85% of the patients showed abatement of the disease, the treatment results in latent cases who received a comparative amount of penicillin should be satisfactory in 85% of cases. A plea is made for periodic follow-up of the other 15%.

Penicillin Treatment of General Paresis.—Gianascol and his colleagues [173] studied the clinical, laboratory, and pathological findings in 14 patients who had been treated for general paresis with 6,000,000 units of penicillin. All patients were examined three and six months after treatment and then yearly until death. Ten of the patients had simple dementing paresis; one had juvenile paresis; one had manic-grandiose psychosis, and two were schizoid. The time between treatment and death ranged from 4 to 85 months. Except for a normal white cell count in four patients, all pretreatment spinal fluid findings were characteristic of untreated paresis. Follow-up spinal fluid findings showed a decrease in white cell count and protein followed by a slow reversion of the spinal fluid test for syphilis and colloidal gold curve to normal. In no case did the spinal fluid findings suggest progression of the disease. Postmortem examination of the brain was carried out in all patients. The macroscopic brain changes were minimal. The brain weight of most patients was below average. The cerebrum appeared atrophic in eight cases. Nine patients manifested some degree of ventricular dilatation. Microscopic findings revealed meningeal fibrosis with minimal lymphocytic and plasma cell infiltration, marginal gliosis, cortical neuron loss, and minimal to moderate disturbance of the architecture of the cortex. Astrocytosis and microglial reaction including presence of rod cells persisted to a mild degree. Perivascular infiltration gradually subsided as the time interval between treatment and death lengthened and was not present in any patient who died 42 or more months after treatment. Proliferation of capillary endothelium persisted mildly following treatment. No uniform correlation could be found between the clinical course, the laboratory data, and the neuropathologic abnormalities at postmortem examination. As the interval between treat-

ment and death lengthened, the neuropathologic findings approached those of inactive paresis, and after 38 months there was no evidence of activity of the syphilitic process in the brain. Timberlake [174] stated that benzathine penicillin G and/or benethamine penicillin G will supersede procaine penicillin G in the treatment of neurosyphilis because of lesser toxicity and lower dosage. It is further averred that the major problem today is adequate early case finding and control.

TREATMENT OF OCULAR SYPHILIS

Topical Cortisone in Syphilitic Interstitial Keratitis.—Horne * made detailed reports of 20 patients (26 eyes) and, later, of 23 patients (29 affected eyes) with syphilitic interstitial keratitis treated with topical cortisone, who were kept under observation for periods ranging from 6 to 39 months after the start of treatment. It is concluded that the correct use of topical cortisone produces results much superior to all previous methods of treatment. It is also concluded that topical cortisone is imperative in the treatment of syphilitic interstitial keratitis. An outline is given of the best way of using it in this condition in the light of personal and recorded experience. On the basis of 20 cases of interstitial keratitis occurring as a result of congenital syphilis treated with cortisone and observed closely for at least one year, North [177] concluded that this preparation has changed this ocular complication from a long and painful illness, with the sequellae of defective vision or blindness, into an acute condition lasting only a few days. It may, except for very acute cases, be used on an outpatient basis. If treatment can be started before corneal infiltration obscures vision, sight need not be impaired at any time.

Treatment of Optic Atrophy.—Among 141 patients with primary optic atrophy observed by Hahn and co-workers [178] after various types of antisyphilitic treatment (metal chemotherapy, malaria without penicillin, penicillin plus malaria, and penicillin without malaria) progression occurred in approximately one-third during the first year, in approximately one-half at two to three years, and in approximately two-thirds at four to five years. Loss of 80% or more of initial visual efficiency occurred in only 10% at one to two years, 15% at four to five years, and 20% at seven to eight years. The study did not permit valid comparison between the effects of the several types of treatment in syphilitic optic atrophy. Deficiencies in basic data on the prognosis in the absence of treatment preclude accurate comparison between the effects of the several treatment methods. The rate of progression after treatment was not apparently significantly influenced by pretreatment spinal fluid cell count. Klauder and Gross [179] also carried out a study of the results of treatment in 104 patients with syphilitic primary optic atrophy. Three schedules of treatment were employed: 4,200,000 units of partially purified sodium penicillin in aqueous solution administered in 7½ days, 3,600,000 units of crystalline penicillin G administered in 7½ days, and 11,000,000 units of penicillin administered in 14 days. Progression or lack of progression of optic atrophy was determined by comparison of visual acuities and peripheral fields before treatment and at three- to six-month intervals following treatment. No significant difference was found in the percentage of unsatisfactory outcome in these three treatment groups. However, the penicillin-treated groups fared better than did a control group of 86 patients treated by chemotherapy. Corticotropin and cortisone were used in the retreatment of six patients whose optic atrophy progressed unfavorably. The authors do not feel that routine use of steroids has been proved to be of value. Fever therapy was administered to 24 patients as part of the initial treatment. Fever therapy did not prevent unfavorable progression or blindness. Metal chemotherapy was used apparently largely for its psychological effect. Data are given on the interval between onset of impaired vision and blindness in 81 patients who, when first seen, were untreated

* References 175 and 176.

and blind. Twenty-eight of these became blind in less than 12 months; thirty-eight, in the 2nd year; ten in the 3rd and 4th years, and three did not become blind until 9 or more years after the onset of impaired vision.

TREATMENT OE CONGENITAL SYPHILIS

The Prevention of Congenital Syphilis.—The best hope of prevention and ultimate eradication of congenital syphilis depends on detection and treatment of previously undetected syphilis during the antenatal period. Morton [180] found that of 42 cases of previously undetected antenatal syphilis, 25 were in the latent stage. Of the 42 pregnancies, 41 ended in live births. There was one miscarriage. The need is emphasized for close cooperation by all concerned in antenatal care if a high percentage of antenatal Wassermann tests is to be performed.

Penicillin Treatment for Early Congenital Syphilis.—Smith and his co-workers [181] present data on 472 children with congenital syphilis who were treated with penicillin, with or without adjunctive bismuth, during the first two years of life. Of these, approximately 40% were followed from 18 to 21 months. Results showed a higher rate of seronegativity in children treated during the first year of life, regardless of amount of penicillin used. The pattern of serologic response was analogous to treatment results in acquired syphilis during the early stages and latency. The highest percentage of seronegativity and the lowest percentage of serologic or clinical failure were found among those receiving 321,000 units or more per 1000 gm. of body weight. Rate of serologic failure was 1.7% among those under 3 months of age at treatment, as compared with 1.1% for those 3 to 5 months of age; no serologic failures among those 6 to 11 months of age, and 5.0% for those 12 to 24 months of age. There was a direct correlation between the age of time of treatment and the per cent remaining positive after treatment. Results showed that the longer the delay in treatment the slower the rate of seroreversal. Bos and his associates [182] also present observations on 26 newborn infants and on one 18-month-old infant who were treated for congenital syphilis with penicillin. The total dose, of from 150,000 to 200,000 units per 1000 gm. of body weight, was usually administered over a period of two weeks. On the first day six doses of 2500 units, on the second day six doses of 5000 units, and on the third day six doses of 7500 units were given, and during the subsequent 11 days the six daily doses were apportioned in such a way that the total of 150,000 or 200,000 units per 1000 gm. of body weight was given. The authors feel that these favorable results justify continuation of the present treatment of congenital syphilis by one course of penicillin. The final evaluation of this treatment requires further observation.

HERXHEIMER REACTION

Herxheimer Reaction in Congenital Syphilis.—Wattiez [183] observed and treated 24 cases of congenital syphilis in the newborn. Five of the infants died during or after penicillin therapy, but in only one case was a Herxheimer reaction considered; the others were all instances of very serious debility from syphilis or some superimposed infection. Enkvist [184] observed fever within three weeks from onset of therapy in 75% of 208 infants with congenital syphilis, but there were no secondary infections. Twenty-five per cent of the infants had fever in connection with a Jarisch-Herxheimer reaction. Among 67 children whose treatment was begun with penicillin the figure was roughly double (55.2%).

TOXIC REACTIONS TO PENICILLIN TREATMENT

The *British Journal of Venereal Diseases,*[185] points out, in a well-documented editorial, the increase in serious and even fatal reactions to penicillin. The use of corticotropin (ACTH), when therapy is imperative, may suppress the reactions. The number of fatal anaphylactic reactions may be small in proportion to the number of penicillin injections administered, but one must

pause when one author reports eight cases (Rosenthal [186]). Various preparations of penicillin are responsible for these reactions (Etter and Merryman [187]; Morrisset [188]), even oral preparations (Eisenstadter and co-workers [189]).

Bell, Rannie, and Wynne [190] have shown by means of experiments on cats that the intravenous injection of procaine penicillin produces reactions of varying severity and sometimes causes death. Necropsy findings suggest that pulmonary embolism plays an important part in the reactions to deliberate intravenous injection. Adverse reactions to intramuscular injections of suspensions of procaine penicillin in man are compared with the experimental findings in cats in relation to time of onset and type of reaction. The authors infer that accidental intravenous injection of suspensions of procaine penicillin is the cause of some of the severe and fatal reactions in man.

Occurrence of the "L. E." Phenomenon in a Patient with a Severe Penicillin Reaction.—Paull [191] treated a patient for pneumonitis and congestive heart failure with digitalis, mercurial diuretics, penicillin, and streptomycin. Penicillin was given for a 12-day period and streptomycin for 10 days. After the therapy the patient developed a "severe skin rash," pruritus, dysphagia, temperature of 101.2 F, and arthralgias of the knees, ankles, shoulders, and left wrist. The peripheral blood contained L. E. cells (low-grade positive). After the symptoms subsided, no L. E. cells were found. Paull states that it is highly improbable that this patient had disseminated lupus erythematosus. As in other conditions (hemolytic anemia, miliary tuberculosis, pernicious anemia, dermatitis herpetiformis, chronic discoid lupus erythematosus, leukemia, generalized moniliasis, and multiple myeloma) the degree of positivity in this instance was low. Haserick has stated that he has never observed a false positive reaction in the 3+ and 4+ group.

Central Nervous System Complications Resulting from Penicillin.—Huber [192] reviews the literature on severe and fatal complications of the central nervous system following administration of penicillin. He observed two patients who died from central nervous complications following intramuscular injection of penicillin. He emphasizes that in neurosyphilis penicillin therapy should be begun with slowly increasing doses or should be preceded by treatment with heavy metals.

SYPHILOID DISEASES

It has become a rather trite observation that the syphiloid diseases, indigenous to this or that country, are no longer a problem of any particular country or area but are a world problem and that knowledge of these exotic diseases is a must for all physicians. This is especially exemplified this year by the report from Manchester by Laird,[193] who noted that the influx of immigrants from West Africa and the West Indies to Manchester has been reflected in the increased number of Negro male patients seen in the venereal disease clinics. A considerable number of these men have positive serological tests for syphilis, and there is evidence in some cases that the serological results arise from childhood infection with yaws in their native land. Laird reports a case of a white child who acquired yaws as a young child in East Africa. It is suggested that in the interpretation of positive serological tests in Negro immigrants yaws should be considered in differential diagnosis.

Treponematosis Control in Thailand.—When the yaws campaign was started in Thailand in 1949, the average prevalence was about 13%.[194] A training laboratory was established at Rajburi. The serologic techniques used and taught were the VDRL slide flocculation test and the standard Kahn test. Meinicke, Kline, and complement-fixation tests were carried out in one or more of the four laboratories established later. PAM was used for treatment of all types of yaws. Up to October, 1952, two injections at three-day intervals were given. Dosages were 4 ml. for those over 10 years of age, 2 ml. for those from 2 to 10 years, and 1 ml.

for those under 2 years. Later, the same amounts were administered in a single injection. Since 1953, the dosages have been increased for those under 10 years of age. By June, 1954, examination had been done in 86.5% of the population, with 12.3% having been treated. A control study of treatment with benzathine penicillin G was done in one village. Lesions healed completely. Scars in patients treated with benzathine penicillin G were softer and smoother than in those treated with PAM.

Treponematoses in Gambia.—Investigations have shown two forms of treponematoses occurring in Gambia, West Africa.[195] These are yaws and another treponemal disease, which shows similarities with the endemic syphilis among the Arabs and the people of Bosnia. This latter disease usually appears first on the mucous membranes at the angles of the mouth in young children or on the tip of the penis in small boys. Lesions contain large numbers of spirochetes morphologically identical with T. pallidum, and the patients give strongly positive Wassermann and Kahn reactions. Secondary manifestations of the disease are florid eruptions on the vulva and in the anal cleft and circularly arranged groups of papules which may coalesce to form rings. The commonest tertiary lesion is a hyperkeratosis of the palms and soles associated at a later stage with depigmentation of the hands and feet. The use of a common drinking cup is prevalent in Gambia, and this is believed to be responsible for passing the disease.

Bacteriologic and Serologic Aspects of Pinta.—In a brief and interesting review article, Rein [196] discusses some of the bacteriologic and serologic aspects of pinta. Treponema carateum, now known to be the causative organism of pinta, is morphologically identical with the treponemes of syphilis, yaws, and bejel, whether examined by the dark-field, electron, or phase microscope. In vitro and in vivo studies show no significant difference in susceptibility to penicillin of the treponemes of venereal syphilis, endemic syphilis, yaws, bejel, and pinta. Clinically, all of the entities in the treponematosis group respond to all of the treponemicidal drugs and antibiotics. However, pinta responds more slowly to penicillin than do the others. Primary and early secondary lesions of pinta disappear 4 to 6 months after treatment, whereas late secondary lesions require from 6 to 12 months for complete healing. However, treponemes disappear from lesions within 6 to 10 hours after a single injection of penicillin. The majority of investigators have been unable to inoculate pinta treponemes into experimental animals. In its late stages, pinta confers immunity against reinfection, but there is apparently no cross immunity against syphilis or yaws. Pinta does not produce prenatal infection or late internal visceral involvement. Most patients with pinta are seropositive. The Kahn "verification test," the euglobulin inhibition procedure of Neurath, the Kahn universal reaction, and the treponemal immobilization test are all incapable of differentiating pinta from the other treponematoses. The high incidence of zone reactions in pinta is pointed out. It has been suggested that these may be due to a blocking antibody. Rein concludes that pinta is similar in many ways to the other treponemal infections.

Fijian Syphilis.—Manson-Bahr [197] reports three cases of congenital, two cases of primary, and one case of meningovascular syphilis in Fijians and a Fijian-Tongan. He presents experimental and clinical evidence to show that the previous absence of recorded syphilis in Fijians favors the existence, amongst communities in which yaws is prevalent, of a relative immunity to naturally acquired syphilis. This relative immunity is breaking down in Fiji as a result of successful yaws treatment.

Njovera.—Willcox [198] has compared the *njovera* of Southern Rhodesia with bejel. He concludes that both conditions are examples of endemic syphilis.

CONTROL OF SYPHILIS

Much progress in the control of syphilis has been recorded, as previously mentioned, during this review period. Although syphilis is still a problem in some areas having low

socioeconomic groups,† definitely continuing downward trends have been recorded in certain of the United States and foreign countries (Minnesota,[201] New York,[202] California,[203] Puerto Rico,[204] Australia,[205] Norway[206]). The prevalence of syphilis in Ceylon[207] and in Palestine,[208] while estimated, is not presented in such a manner as to indicate trends.

Case Finding.—Case finding[209] has been discussed from many angles; in fact, this phase of syphilis control presented one of the most interesting and fruitful fields for investigation in this review period. Among the subjects covered are the following: venereal disease among teen agers, role of the dentist in the detection of congenital syphilis, premarital examinations, prenatal health examination legislation, syphilis in industry, syphilis in agricultural migrants, venereal disease contacts of merchant seamen in the Navy and other military personnel, and regulation of prostitution. A novel, yet fruitful, case-finding project which one of us (I. L. S.) conducted under the name "Operation Streetcorner" was recently completed.

Venereal Disease Among Teen Agers.—From morbidity data classified by age for all syphilis and gonorrhea cases reported in the calendar year 1953, collected from state and city health departments, Donohue and his co-workers[210] report that venereal disease is but one of the problems to which our less protected and therefore less privileged youth is exposed. They show that there is a significant positive association between the infectious venereal disease rate among teen agers and juvenile delinquency, that there is a positive association between the percentage of infectious venereal disease among female teen agers and the number of illegitimate births, that there is a significant association between venereal disease in teen age mothers and fetal death, that the higher the percentage of teen agers in school the lower the venereal disease attack rate among the age group, and that there exists a significant positive association between venereal disease and low financial status. The peak morbidity is at the 20 to 24 year age group. The abrupt increase in cases at ages 15 to 19 years indicates how serious the venereal disease problem is after age 14. Among persons under 20 years of age an incidence of 22.4% of infectious disease is reported. Although infectious venereal disease is diagnosed more frequently among males than among females because of more obvious signs or painful symptoms in the male, nevertheless blood-testing surveys have shown that the two sexes have equal syphilis prevalence rates. Under age 20, females of both races have a higher proportion of cases than do males, and for each sex the rate for nonwhites is higher than the rate for whites. Infectious venereal disease is sexually acquired at a much earlier age than has been realized. The upward swing begins in females at age 12 and in males at age 14. Females have a higher proportion of cases than males in the earlier years up to age 17, at which age the percentage in males becomes higher than in females.

Role of the Dentist in the Detection of Nondental Disease.—Whereas the general practitioner is not usually consulted until symptoms of illness appear, the dentist sees people who are, for the most part, apparently healthy and is often the first to see pathologic changes in the body, according to Pinckney.[211] The dentist has a moral obligation, therefore, to participate in public health programs for the detection of latent diseases. Among these which might be seen first by the dentist are tuberculosis and syphilis, especially congenital syphilis. The dentist's role in finding congenital syphilis is discussed, and the literature shows that he can be of great value in the detection of that condition. That he is not is due to a lack of recognition by the dentist himself of his potentialities in this respect. Of the 7459 instances of congenital syphilis discovered in California in 1952, at least half of them might have been discovered previously by dentists because of the presence of oral pathology findings; yet there is no record of even one case having been so discovered.

† References 199 and 200.

Many other conditions which might first be detected by dentists who are alert to their diagnostic significance are mentioned.

Premarital Examinations.—The premarital laws in 34 states bring the bride and groom to a physician. The laws vary from state to state, but they are all designed to prevent the transmission of venereal disease. Kavinoky [212] describes in detail how, with the addition of a few simple procedures and explanations by the physician, the examination can also prevent many marital maladjustments. The physician can give the couple such information about their own sexual organs that they can consummate their marriage without undue trauma. Fortunately, many parents, religious leaders, and educators are turning to the physician for medical help in preventing annulments and divorces. The premarital examination plays a large part in this education.

Prenatal Health Examination Legislation.—In March, 1938, the prenatal health examination bill,[213] the first of its kind, became a law in New York State. At present 42 states, Hawaii, the Virgin Islands, and Alaska have enacted prenatal health examination laws. Only Alabama, Maryland, Minnesota, Mississippi, Tennessee, Wisconsin, and the District of Columbia do not have any law covering this type of health protection.

The prenatal health examination laws are confined to blood serologic tests for syphilis. They are directed to the physician or midwife attending the pregnant woman. In Georgia and North Carolina not only is it the responsibility of the physician attending a pregnant woman to perform a serologic test for syphilis but it is also the responsibility of the pregnant woman to report to a physician and to request such a test.

All 42 states require that the physician submit a blood sample to a state-approved laboratory. In 33 states the serologic tests are free. In 13 states penalties are exacted of the attending physician for violation of the law. In eight states penalties are exacted unless the woman refuses to submit to a serologic test for syphilis.

The number of cases of congenital syphilis in the continental United States dropped 47.5% from 1941 to 1952, while the number of early syphilis cases declined 82.4%. In 1952, a total of 9240 cases of congenital syphilis were reported in the United States. This was a decline of 28% from the number reported in 1951.

Studies have been made in California, North Carolina, Baltimore, Atlanta, and Massachusetts to determine the probable causes for the persistence of a preventable infection such as congenital syphilis. In Massachusetts the following factors were found: (*a*) inadequate treatment of infected mothers; (*b*) infection of mother subsequent to initial blood test; (*c*) reinfection or relapse of infected mother; (*d*) ignorance and carelessness of mothers in not seeking prenatal care; (*e*) failure on the part of physicians to perform a blood test for syphilis. It is necessary to institute intensive case-finding programs to help eliminate the backlog of congenital syphilis cases. These programs should be aimed at groups in areas where syphilis prevalence rates are high and at children whose mothers did not have serologic tests during pregnancy. The birth certificates should be examined, as 31 states require a statement as to whether or not a blood test was made during pregnancy. A study of birth certificates filed in 1948 in South Carolina showed that 37% of tests were not performed or not reported.

Syphilis in Industry.—It is Graham's [214] opinion that the current low morbidity of syphilis does not suggest a valid reason for doing routine preemployment serologic tests. However, in certain socioeconomic and geographically located groups where the known incidence of the disease is higher than average such routine testing may be indicated.

Downing [215] collected much interesting material on the present problem of syphilis in industry for his report to the American Academy of Dermatology and Syphilology. Although 18 states and the District of Columbia reported an increase in infectious syphilis in 1953, the federal government recently drastically cut its budget and re-

duced the grants-in-aid for venereal disease control to the states and local communities. This was short-sighted economy. Many states and communities no longer provide epidemiological services in tracing contacts of persons with active syphilis. The authorities have lost sight of the fact that there is an infectious reservoir of venereal disease still remaining in our communities. The sexual mores of our people, being what they are, will further increase this reservoir. If control efforts are relaxed through overoptimism and penny-pinching and if the present level of sexual promiscuity persists, one can predict epidemics of these diseases in the future. The curtailment of federal grants to the states was reflected in industry. Many state health departments that had previously performed serologic tests for syphilis without charge for industrial physicians ceased to do so. Industrial medical departments were unwilling to use their meager budgets to have these tests run by private laboratories. As a result, many industries stopped performing these tests. One requirement for certification by the American Academy of Occupational Health is routine serologic examination. Several medical directors of plants have stated to Dr. Downing that they believe that the restricted budgetary measures are short-sighted, and, despite the dramatic advance in therapy, the incidence of syphilis is increasing in the industrial population.

Dr. Downing touched on an extremely important and oft-recurring problem. It was reported that a large number of industries in Cincinnati had an employment policy that barred from work any person who had a reactive serologic test for syphilis, on the fallacious assumption that this indicated acute syphilis. This matter was discussed with personnel managers, and the formulation of this archaic policy was blamed on advisors of the company. These officials asked how it was known that antibiotics really cured syphilis and declared that other persons would refuse to have personal contact with a man known to have syphilis and that they could not take chances with such a man. Steps were taken to enlighten such employers. It was agreed that nobody should be refused employment solely because of a positive serologic test for syphilis. The interpretation of the serologic status of a person can be made only by a physician and may occasionally be a complex problem, requiring the services of an expert. Under no circumstances should the employability of a person with a reactive serologic test for syphilis be determined by lay persons who pass on the other qualifications of the prospective employee. The certificate of a physican that the seropositive person is noninfectious and physically employable should suffice.

Venereal Disease in Agricultural Migrants.—Shepard and Page [216] estimated that 16,000 migrant agricultural workers enter New Jersey annually. The group is made up mainly of Jamaicans, Puerto Ricans, and southern Negroes. Of an estimated 6000 Negroes, 3401 were given serologic tests for syphilis. A total of 19 cases of primary and secondary syphilis were found, as well as 135 cases of early latent syphilis and 198 cases of gonorrhea. On the basis of the results obtained in this group, it is recommended that serologic surveys and other control measures be expanded wherever possible to include the entire domestic migrant population.

Watson [217] describes some aspects of the work of the Intergovernmental Committee for European Migration Liaison Mission in Greece. The workers are selected first as to their ability as rural workers and then as to their physical fitness. The procedure for medical examination of the Intergovernmental Committee for European Migration (ICEM) is outlined. Kahn tests were performed on all migrants over 16 years of age as a routine procedure. Of 11,053 migrants examined, 178 gave positive Kahn reactions and 63 had doubtful reactions. The ultimate incidence of positive reactors is thus approximately 1.9%. For reasons given, no conclusion can be drawn from these figures as to the true incidence of syphilis in Greece. Positive reactors are notified, and immigration is forbidden until the reaction is confirmed and treatment has been received. Confidential

lists of such persons are submitted to the Department of Hygiene in Athens and to health centers in the district from which the persons originally came. Parallel procedures are carried out in finding and treating tuberculosis, echinococcosis, entamebiasis, trachoma, and pterygia. Persons with rheumatic fever were rejected outright, and those with hernias were accepted after proper surgery. Cooperative procedures with Australian authorities are described.

Venereal Disease Contacts of Merchant Seamen.—The Division of Foreign Quarantine, in cooperation with the Division of Venereal Disease, Public Health Service,[218] conducted a study of venereal disease contacts among merchant seamen from June 1, 1951, to Nov. 30, 1951. The purpose of the study was to determine which seaports of the world are the principal foci of infection.

A contact study report was completed for each seaman who had been treated for venereal disease during the voyage to the United States or who had clinical symptoms of venereal disease on arrival. In the six-month study, 2426 infected seamen reported 4364 sex contacts in ports throughout the world. There were 1953 cases of gonorrhea and 225 cases of syphilis.

The study shows that Japan represents the greatest venereal disease problem, with 1654 contacts (37.9% of the total 4364 sex contacts). Europe was next, with 17.5%, and the United States was sixth, with 4.2%. Of 119 merchant seamen with infectious syphilis admitted in 1952-1953 to the Staten Island Public Health Service Hospital, 34 reported contacts both in the United States and in foreign countries. Of this number, 31 were Americans. So it would appear that the American seaman may be the principal agent among seafaring personnel in carrying venereal disease between foreign countries and the United States.

Preliminary Statistics of Navy Medicine.—The incidence of venereal disease in the Navy[219] increased by 15% over 1953 levels, to 47.5 per 1000. In noncontinental shore-based personnel the rate increased from 86.6 to 106.2 per 1000 in 1954, an increase of 22%. Gonococcic infections were responsible for this rise. Venereal disease in ship personnel showed a lesser increase over 1953, from 64.6 to 69.4 per 1000, while sailors in continental United States had a lower rate than in 1953, dropping to 16.0 per 1000. The incidence of nongonococcic urethritis rose from 14.3 to 20.4 per 1000, an increase of more than 40%. The rise occurred exclusively in noncontinental areas and aboard ships; the rate for continental United States remained at 2 per 1000. The ratio of gonococcic infections to nongonococcic urethritis was 7:1 in continental United States, while in noncontinental shore-based areas the ratio was 2:1 and for shipboard personnel it was 1.5:1. Most of the nongonococcic urethritis is being reported from the Far East and among shipboard personnel of the Pacific fleet.

Special Problems in the Diagnosis and Management of Syphilis in Military Personnel.—In an article describing the special problems in the diagnosis and management of syphilis in military personnel, Rein, Kostant, and Kimmelman[220] review basic schedules of the various stages of syphilis, indications of retreatment, false positive reactions vs. latent syphilis, and the management of the contacts of patients with proved early syphilis. The last subject has been discussed many times without unanimity of opinion. Rein concludes his short discussion in this way: "Rule: In handling the syphilis contact, assume that he has acquired the disease, administer adequate 'pre-primary treatment', and enforce clinical and serologic re-examinations."

From the public health point of view, there is no doubt that the treatment of all syphilis contacts is indicated, because it would serve to reduce the incidence of new clinical infections. Methods should be enforced to ensure the patient's return for clinical and serologic rechecks and at least one spinal fluid examination, in order to detect and treat possible relapses and reinfections.

Legalized Prostitution.—Lentino[221] medically evaluated a system of legalized prostitution by studying the method of operation,

police control, and medical control of houses of prostitution in Leghorn, Italy. He found that police control is rigid but that medical control is inadequate, although each prostitute is examined every second day. This inadequacy is due to the difficulty of diagnosing venereal disease in women. This study proves untrue the argument by the proponents of legalized prostitution that it insures protection against venereal disease. The legislation designed to control prostitution and venereal disease in France is reviewed by Watson.[222] The prewar and Vichy government system of licensing brothels and individual prostitutes is described, and the effect of the postwar abolition of this system on public health is discussed. The responsibilities of medical practitioners and the police are described. The new program has aroused acute controversy in France. The medical profession dislike compulsory notification of infectious cases and the legal duty of carrying out epidemiological investigations for which they have neither the time nor the facilities. Reliable statistics on prostitution and morbidity from venereal diseases are difficult to obtain, but insofar as they are available they have been used to assess the claims of the supporters and the opponents of the new policy.

"Operation Streetcorner."—In May and June, 1954, the City of Philadelphia ‡ conducted a mass blood-testing program in sections of the city where previous epidemiologic studies had suggested a high prevalence of syphilis. Testing was done on street corners and house-to-house. A total of 35,402 persons were tested, of whom 3788 (10.7%) were found to have reactive or weakly reactive tests. Within 10 weeks, approximately 2700 (75%) had come under medical supervision. About 500 are under care of private physicans. Of these, 114 were found to be infected with syphilis and placed under treatment, 31 were found not infected after further study, 7 had previously received adequate therapy, and about 350 are still under observation and final reports have not yet been received by the health department. Of the cases seen in the city clinics there were 1 secondary, 51 early latent, 602 late latent, 1 cardiovascular, 97 central nervous system, 10 congenital, 328 previously adequately treated, and 340 not infected. In terms of dollars and cents, to say nothing of misery and suffering, in preventing disability, this study has paid for itself many times over.

The "Precontemporary" Syphilitic Defaulter.—Morton [225] gives details of an attempt made to persuade 368 patients, who defaulted from antisyphilitic treatment during the years 1941-1950, to reattend. Two years after completion of recall it can be stated that those required to make regular attendances have nearly all done so.

‡ References 223 and 224.

REFERENCES

1. Shaffer, L. W.: Venereal Disease Control at the Crossroads, Am. J. Syph. **38**:349-353 (Sept.) 1954.

2. The War Against VD Must Continue, editorial, Am. J. Pub. Health **44**:928-929 (July) 1954.

3. Beerman, H.; Schamberg, I. L.; Nicholas, L., and Katzenstein, L.: Syphilis: Review of the Recent Literature, A. M. A. Arch. Int. Med. **95**: 256-319 (Feb.) 1955.

4. Moore, J. E.: The Passing of the American Journal of Syphilis, Am. J. Syph. **38**:487-488 (Sept.) 1954.

5. Syphilis, Editorials and Comment, J. A. M. A. **157**:727 (Feb. 26) 1955.

6. Editorial, A. M. A. Arch. Dermat. **71**:1 (Jan.) 1955.

7. Dallenbach, F. D.: Diagnostic Problems: Presentation of Case, J. A. M. A. **158**:479-480 (June 11) 1955.

8. Roberg, N.: Diagnostic Problems, Comment, J. A. M. A. **158**:480-481 (June 11) 1955.

9. Progress Against Syphilis, Science News, Science **121**:230 (Feb. 18) 1955.

10. Syphilis, Washington News, J. A. M. A. **156**:14 (Sept. 25) 1954.

11. Rein, C. R.: Chemotherapy of Syphilis and Gonorrhea, editorial, Antibiotic Med. **1**:4 (Jan.) 1955.

12. Extract from the Annual Report of the Chief Medical Officer for the Year 1953, Brit. J. Ven. Dis. **31**:44-47 (March) 1955.

13. Late Effects of Syphilis, Annotation, Brit. M. J. **2**:923 (Oct. 16) 1954.

14. Treatment of Syphilis, Editorials and Comments, J. A. M. A. **156**:894 (Oct. 30) 1954.

15. Syphilis, Bull. World Health Organ. **10**: 507-626, 1954.

16. White, A. (pseudonym): They Said I Had Syphilis, Saturday Evening Post, April 30, 1955, pp. 23 and 134-138.

17. Clark, E. G.: Natural History of Syphilis and Levels of Prevention, Brit. J. Ven. Dis. **30**: 191-197 (Dec.) 1954.

18. Syphilitic Venereal Disease, 16 mm. color sound film, showing time 25 minutes, prepared by Evan W. Thomas, M.D., produced in 1954 by Sturgis Grant Productions, New York, for and procurable on loan from E. R. Squibb & Sons, 745 Fifth Ave., New York 22.

19. Nabarro, D.: Congenital Syphilis, London: Edward Arnold & Co. 1954.

20. Welch, H., in collaboration with Braley and others: Principles and Practice of Antibiotic Therapy, specially edited by Felix Marti-Ibanez, New York, Medical Encyclopedia, Inc., 1954.

21. Willcox, R. R.: Perspectives in Venereology, 1953, Bull. Hyg. **29**:541-562 (June) 1954.

22. Willcox, R. R.: Further Progress in Venereology, Brit. J. Ven. Dis. **30**:216-238 (Dec.) 1954.

23. Wortmann, F.: Syphilis Juli 1953 bis Juli 1954, Dermatologica **109**:306-333, 1954.

24. Tilley, R.: Syphilis, New England J. Med. **252**:308-312 (Feb. 24); 351-356 (March 3) 1955.

25. Schnitzer, R. J., and Grunberg, E., Conference Co-Chairmen, and others: Paul Ehrlich Centennial, Ann. New York Acad. Sc. **59**:141-276 (Sept. 23) 1954.

26. Pinkus, H. K. B.: In Commemoration of the 100th Anniversary of the Birth of Paul Ehrlich, Am. J. Clin. Path. **24**:751-754 (July) 1954.

27. Hollander, A.: Fiftieth Anniversary of the Discovery of the Spirochaeta Pallida, A. M. A. Arch. Dermat. **71**:289-292 (March) 1955.

28. Richter, J. H.: Albert Neisser, A. M. A. Arch. Dermat. **71**:92-94 (Jan.) 1955.

29. Cole, H. N.; Harkin, J. C.; Kraus, B. S., and Moritz, A. R.: Pre-Columbian Osseous Syphilis, A. M. A. Arch. Dermat. **71**:231-238 (Feb.) 1955.

30. Harrison, L. W.: Some Lessons Learnt in 50 Years' Practice in Venereology, Brit. J. Ven. Dis. **30**:184-190 (Dec.) 1954.

31. Durel, P., and Sausse, A.: Rappel de l'origine de la souche tréponèmique Nichols: Conservation de sa virulence pour l'homme après 40 ans, Bull. Soc. Franç. dermat. et syph. **61**:139-142 (March-April) 1954.

32. Lejman, K.: Involutional Changes of Treponema Pallidum During Penicillin Treatment in Man, Acta dermat.-venereol. **34**:293-304, 1954.

33. Morton, H. E., and Ford, W. T.: Preliminary Observations of the Action of Penicillin on Treponema Pallidum in Vivo, Am. J. Syph. **37**:529-535 (Nov.) 1953.

34. Beamer, R., and Firminger, I.: Improved Methods for Demonstrating Acid-Fast and Spirochetal Organisms in Histologic Sections, Lab. Invest. **4**:9-17 (Jan.) 1955.

35. Tauber, H.: Free Amino Acids and Glutathione of Normal and Syphilitic Rabbit Testes, Proc. Soc. Exper. Biol. & Med. **86**:838-842 (Aug.-Sept.) 1954.

36. Hollander, D. H., and Turner, T. B.: The Role of Temperature in Experimental Treponemal Infection, Am. J. Syph. **38**:489-505 (Nov.) 1954.

37. Turner, T. B., and Hollander, D. H.: Studies on the Mechanism of Action of Cortisone in Experimental Syphilis, Am. J. Syph. **38**:371-387 (Sept.) 1954.

38. Aavik, O. R.: Studies on the Prophylactic Effect of Locally Applied Antibiotics in Experimental Syphilis, J. Invest. Dermat. **23**:497-501 (Dec.) 1954.

39. Peters, J. J.; Peers, J. H.; Olansky, S.; Cutler, J. C., and Gleeson, G. A.: Untreated Syphilis in the Male Negro: Pathologic Findings in Syphilitic and Non-Syphilitic Patients, J. Chron. Dis. **1**:127-148 (Feb.) 1955.

40. Shafer, J. K.; Usilton, L. J., and Gleeson, G. A.: Untreated Syphilis in the Male Negro: A Prospective Study of the Effect on Life Expectancy, Pub. Health. Rep. **69**:684-690 (July) 1954.

41. Olansky, S.; Simpson, L., and Schuman, S. H.: Untreated Syphilis in the Male Negro: Environmental Factors in the Tuskegee Study of Untreated Syphilis, Pub. Health Rep. **69**:691-698 (July) 1954.

42. Du Pasquier, P.: Les tests cutaneès dans le diagnostic de la syphilis, J. méd. Bordeaux **131**: 276-284 (March) 1954.

43. Expert Committee on Venereal Infections and Treponematoses, Subcommittee on Serology and Laboratory Aspects: Third Report, World Health Organization Technical Report Series, No. 79, Geneva, World Health Organization, October, 1954, pp. 1-50.

44. Stout, G. W.; Harris, A., and Olansky, S.: Developments and Trends in the Serodiagnosis of Syphilis, Am. J. M. Technol. **20**:269-276 (Sept.-Oct.) 1954.

45. Sanford, A. H.: Serodiagnostic Tests, Laboratory Notes, Postgrad. Med. **16**:A52-A54 (Sept.) 1954.

46. Kahn, R. L.: Serology of Syphilis Based on Recent Observations, Brit. J. Ven. Dis. **30**:124-140 (Sept.) 1954.

47. Stout, G. W., and Harris, A.: The Role of the State Laboratory in Statewide Improvement and Standardization of Syphilis Serology, Pub. Health Lab. **12**:112-119 (Sept.) 1954.

48. Nakamura, K., and Ichizaka, K.: Comparative Studies on Serological Tests for Syphilis, Bull. World Health Organ. **11**:995-1005, 1954.

49. Sharlit, H., and Rein, C. R.: A New Procedure for Evaluating Lecithin Preparations in Serodiagnostic Tests for Syphilis, Am. J. Syph. **38**:313-317 (July) 1954.

50. Pirilä, V.: Clinical Evaluation of Sitolipin in VDRL Tests for Syphilis, Acta demato-venereol. **34**:341-352, 1954.

51. Schmidt, H., and Lundbach, H.: Cardiolipin Antigen: V. Studies on the Maturation Phenomenon, Acta path. et microbiol. scandinav. **34**:509-517, 1954.

52. Price, I. N. O.: A Note on the Specificity of Cardiolipin and Standard Antigens in Testing Sera for Syphilis, Brit. J. Ven. Dis. **30**:210-211 (Dec.) 1954.

53. Osler, A. G.; Hardy, P. H., and Sharp, J. T.: The Fixation of Complement by Human Sera and Alcoholic Extracts of Human Cardiac Tissue, Am. J. Syph. **38**:554-566 (Nov.) 1954.

54. Klein, S. J.; Konwaler, B. E., and Leiby, G. M.: Cardiolipin Antigen in the Kolmer-Wassermann Test for Syphilis, Am. J. Syph. **38**:318-329 (July) 1954.

55. Ruge, H.: Quantitative Auswertung alternde Wa. R.-Seren mittels Cardiolipin, Ztschr. Hyg. **139**:43-54, 1954.

56. Kline, B. S.: Cardiolipin, Synthetic L-a-Dimyristoyl Lecithin Antigen in the Serodiagnosis of Syphilis, Am. J. Syph. **38**:578-582 (Nov.) 1954.

57. Kline, B. S.: Pure Lecithin in Serodiagnosis of Syphilis: Chemically Pure Recrystallized Synthetic L-a-Dimyristoyl Lecithin as Antigenic Component with Cardiolipin, Am. J. Clin. Path. **24**: 850-867 (July) 1954.

58. Bollinger, D.: Zur Spezifität und Empfindlichkeit der Cardiolipin-Mikroflockungsreaction, Dermatologia **109**:75-85 (Aug.) 1954.

59. Fromm, G.: Spirochäten Antigene in der Serodiagnostic der Syphilis, Ärtzl. Wchnschr. **9**: 639-641 (July 2) 1954.

60. Rappaport, R., and Stark, G. J.: A Stained Cardiolipin Antigen for the Serodiagnosis of Syphilis, Acta med. orient. **13**:109-113 (May-June) 1954.

61. Greenburgh, H., and Stephens, B. J.: The Victoria Blue (Berger Kahn) Flocculation Test for the Serological Diagnosis of Syphilis, Guy's Hosp. Rep. **103**:174-181, 1954.

62. Boulger, L. R., and Cannon, D. A.: Comparison of the Ide and Harris (VDRL) Slide Flocculation Tests in Nigeria, Brit. J. Ven. Dis. **31**:40-43 (March) 1955.

63. Schmid, E., and Velaudapillai, T.: VDRL Slide Flocculation Reaction for Syphilis Performed on Active Sera, Brit. J. Ven. Dis. **31**:37-39 (March) 1955.

64. Hauser, G. H.; Godelfer, L., and Edwards, D.: A Study of the New Reference Microflocculation Test for Syphilis, Pub. Health Lab. **12**:89-91 (July) 1954.

65. Karim, M. A.: Filter Paper Test in the Diagnosis of Syphilis, Indian J. Ven. Dis. **20**:159-160 (Oct.-Dec.) 1954.

66. Evans, A. J.: Use of the Price Precipitation Reaction in Northern Rhodesia, Brit. J. Ven. Dis. **30**:212-213 (Dec.) 1954.

67. Rein, C. R., and Kelcec, L. C.: The Value of Merthiolated Sera in Evaluation Surveys, Am. J. Syph. **38**:308-312 (July) 1954.

68. Affleck, M. N., and Allen, R. H.: The Preparation of Positive Control Serum for Use in the Serodiagnosis of Syphilis Employing Reagin-like Antibodies Produced in the Rabbit, Am. J. Syph. **38**:567-571 (Nov.) 1954.

69. Kolmer, J. A. and Lynch, E. R.: Use of Calcium Saline Solution in Kolmer Complement-Fixation Test, Am. J. Clin. Path. **24**:946-953 (Aug.) 1954.

70. Kolmer, J. A., and Lynch, E. R.: Anticomplementary Reactions in Complement-Fixation Tests for Syphilis: A Modified Sachs Method for Cerebrospinal Fluid, Am. J. Clin. Path. **25**:102-108 (Jan.) 1955.

71. Karim, M. A.: Anticomplimentary Serum in Modern Modified Wassermann Reaction, Indian J. Ven. Dis. **20**:160-161 (Oct.-Dec.) 1954.

72. Gelperin, A.: The Anticomplementary Reaction in Syphilis Serodiagnosis, Am. J. Syph. **38**: 304-307 (July) 1954.

73. Coleman, R. D., and Appelman, M. D.: Sequestrene Oxalate, Citrate and Treburon: The Effect of These Anticoagulants upon Serodiagnostic Tests for Syphilis, Am. J. Syph. **38**:572-577 (Nov.) 1954.

74. Browne, A. S.; Michelbacher, M. M., and Coffey, E. M.: Effect of Calcium Ion on the Kolmer Complement-Test, Am. J. Clin. Path. **24**:934-945 (Aug.) 1954.

75. Bossak, H. N.; Harris, A., and Olansky, S.: Effect of Room Temperature on Serologic Tests for Syphilis, Brit. J. Ven. Dis. **31**:33-36 (March) 1955.

76. Rein, C. R.; Schwartz, S., and Kelcec, L. C.: Suitability of Heparinized Plasma and Deheparinized Serum in Serodiagnostic Tests for Syphilis, Am. J. Syph. **38**:405-407 (Sept.) 1954.

77. Coleman, P. N.: Concentration of the Cell Suspension in the Wassermann Test, Brit. J. Ven. Dis. **30**:141-143 (Sept.) 1954.

78. Mitra, A. K.; Biswas, S. K.; Sen, S., and Bhattachargee, N. C.: A Preliminary Report on the False Reactions in S. T. S. with Flocculation, Indian J. M. Res. **42**:333-344 (July) 1954.

79. Magnuson, H. J.: Interpretation of Positive Serologic Tests for Syphilis in Clinically Negative Patients, J. Michigan M. Soc. **53**:744-748 (July) 1954.

80. Kolmer, J. A.: The Problem of False Negative Serologic Reactions in Syphilis, Editorial, Philadelphia Med. **50**:29 (Aug. 13) 1954.

81. Kolmer, J. A.: False Positive Serologic Reactions in Syphilis, Editorial, Philadelphia Med. **49**:1325 (June 26) 1954.

82. Moore, J. E., and Lutz, W. B.: The Natural History of Systemic Lupus Erythematosus: An Approach to Its Study Through Chronic Biologic False Positive Reactors, J. Chron. Dis. **1**:297-316 (March) 1955.

83. Schmidt, H.: Cardiolipin Antigen: IV. Incidence of Positive Sero Reactions for Syphilis in "Normal" Persons, Acta dermat.-venereol. **34**: 159-168, 1954.

84. Jeffriss, F. J. G.: The Doubtful Syphilitic Blood Test in Pregnancy, Brit. M. J. **2**:1200-1201 (Nov. 20) 1954.

85. Simpson, R. G.: The Relation of Lymphogranuloma Venereum to Syphilis and to Falsely Positive Serologic Tests for Syphilis, Am. J. Syph. **38**:422-428 (Sept.) 1954.

86. De Almeida, J. O.; De Freitas, J. L. P., and Brandao, H.: Complement Fixation Test with a Triple Antigen for Syphilis, Tuberculosis, Leprosy, or Chagas' Disease in Blood Banks, Am. J. Trop. Med. **3**:490-494 (May) 1954.

87. De Almeida, J. O.; Souza Lima L., and Carvalho, R. P. S.: The Value of the Quantitative Complement-Fixation Test for Syphilis in Leprosy, Am. J. Trop. Med. **4**:41-46 (Jan.) 1955.

88. Haserick, J. R.: Modern Concepts of Systemic Lupus Erythematosus: A Review of 126 Cases, J. Chron. Dis. **1**:317-334 (March) 1955.

89. Tumulty, P. A.: The Clinical Course of Systemic Lupus Erythematosus, J. A. M. A. **156**: 947-953 (Nov. 6) 1954.

90. Hanrahan, G. C.: Three Cases of Disseminated Lupus Erythematosus with Psychosis, Canad. M. A. J. **71**:374-377 (Oct.) 1954.

91. Allison, A., and Dick, A.: False-Positive Serologic Reactions in Virus Pneumonia, Lancet **2**:364-365 (Aug. 21) 1954.

92. McCleod, C. P., and Stokes, P. S.: Agglutination of Treponema Pallidum by Reagin Antibody, Pub. Health Rep. **70**:379-383 (April) 1955.

93. Anderson, R. I.; Kent, J. F., and Sanders, R. W.: Frozen Syphilomatous Rabbit Testes as Source of Treponema Pallidum for the Immobilization (TPI) Test for Syphilis, Am. J. Syph. **38**:527-530 (Nov.) 1954.

94. Hollander, D. H., and Nell, E. E.: Improved Preservation of Treponema Pallidum and Other Bacteria by Freezing with Glycerol, Appl. Microbiol. **2**:164-170 (May) 1954.

95. Boak, R. A., and Miller, J. N.: A Simple Medium for Maintaining the Viability of Treponema Pallidum in the Treponema Pallidum Immobilization Test, Am. J. Syph. **38**:429-433 (Sept.) 1954.

96. Ajello, G.; Portnoy, J.; Logan, L., and Olansky, S.: Studies of the Treponema Pallidum Immobilization (TPI) Test, Am. J. Syph. **38**: 288-294 (July) 1954.

97. Ledbetter, R. K., Jr., and Cumming, R. J.: Use of Streptomycin to Combat Contamination of Treponema Pallidum Suspensions in the TPI Test, Brit. J. Ven. Dis. **30**:214-215 (Dec.) 1954.

98. Borel, L. J., and Daguet, G. L.: Streptomycin et test d'immobilisation des tréponèmes, Semaine hôp. Paris **31**:1-2 (Feb. 10) 1955.

99. Kolmer, J. A.: The Treponema Pallidum Immobilizing Test in the Serology of Syphilis, editorial, Philadelphia Med. **49**:1397 (July 17) 1954.

100. Elkerton, L. E., and Smith, H. B.: The TPI Test in a Routine Public Health Laboratory Service, Pub. Health Lab. **12**:48-52 (May) 1954.

101. Ledbetter, R. K.: The Practicability of the Treponema Pallidum Immobilization Test on a Service-Wide Basis in the United States Navy, Am. J. Syph. **38**:522-526 (Nov.) 1954.

102. Boak, R. A.; Miller, J. N., and Carpenter, C. M.: The Reproducibility of Results of the TPI Test, Am. J. Syph. **38**:434-436 (Sept.) 1954.

103. Olansky, S.; Harris, A.; Edmundson, W. F., and Rambo, D S.: Negative Kahn Standard and Positive VDRL Slide Tests for Syphilis: Clinicoserologic Evaluation of Preselected Patients, A. M. A. Arch. Dermat. & Syph. **70**:282-288 (Sept.) 1954.

104. Vaisman, A.; Hamelin, A., and Vaisman, H.: Trois années de pratique du test d'immobilisation du Treponema Pallidum (méthod de Nelson et Mayer), Presse méd. **62**:1074-1075 (July 17) 1954.

105. Harris, A.; Olansky, S., and Bossak, H. N.: Comparative Reactivity of the VDRL Slide and Other Tests for Syphilis in Random Population Groups (Including Treponema Pallidum Immobilization Test), Am. J. Syph. **38**:295-303 (July) 1954.

106. Edmundson, W. F.; Ackerman, J. H.; Gutierrez-Salinas, E., and Olansky, S.: Study of the TPI Test in Clinical Syphilis, A. M. A. Arch. Dermat. & Syph. **70**:298-301 (Sept.) 1954.

107. Kern, A. B.: Treponema Pallidum Immobilization Test in the Evaluation of Patients with Positive Serologic Tests for Syphilis, New England J. Med. **251**:807-810 (Nov. 11) 1954.

108. Ruge, H.: Der Nelson-Mayer Test für Syphilis, Medizinische **7**:269-270 (Feb. 12) 1955.

109. Edmundson, W. F.; Kamp, M., and Olansky, S.: Study of the TPI Test in Clinical Syphilis: II. Comparison with the VDRL Slide Test in Treated Early Symptomatic Syphilis, A. M. A. Arch. Dermat. **71**:384-386 (March) 1955.

110. Nielsen, H. A.: Clinical Value of the TPI Test, Acta dermat.-venereol. **34**:102-109, 1954.

111. Tramier, G., and Ranque, J.: Intérêt de l'épruve d'immobilisation du Tréponème dans l'étude de la syphilis familiale, Presse méd. **63**: 515-518 (April 6) 1955.

112. Zellmann, H. E.: The Specificity of the Treponemal Immobilization Test, Am. J. Syph. **38**:506-521 (Nov.) 1954.

113. Edmundson, W. F.; Olansky, S.; Wood, C. E., and Kamp, M.: Study of the TPI Test in Clinical Syphilis: III. Late Syphilis, A. M. A. Arch. Dermat. **71**:387-390 (March) 1955.

114. Wheeler, A. H.; Van Goor, K., and Curtis, A. C.: Treponemal Immobilization and Standard Test Reactions in Suspected Biologic False Positive Sera, Am. J. Syph. **38**:437-446 (Sept.) 1954.

115. MacPherson, D. J.: Ledbetter, R. K., Jr., and Martens, V. E.: Test for Immobilization of Treponema Pallidum: Correlation with Some of the Standard Serologic Tests for Syphilis, Am. J. Clin. Path. **25**:89-92 (Jan.) 1955.

116. Wilkinson, A. E.: Studies on the Treponemal Immobilization Test, Brit. J. Ven. Dis. **30**:144-155 (Sept.) 1954.

117. Eversole, U. H., and Rokowski, W. J.: Spinal Puncture Headache, California Med. **81**: 59-64, 1954.

118. Flodén, C. H.: Cerebrospinal Fluid Protein in Syphilis: A Methodological and Clinical Study Based on the Izikowitz Method for Fractional Protein Determination, and a Comparison with Paper Electrophoretic Protein Determination, Acta dermat.-venereol. (Supp. *32*) **35**:1-184, 1955.

119. Cutler, J. C.; Bauer, T. J.; Price, E. V., and Schwimmer, B. H.: Comparison of Spinal Fluid Findings Among Syphilitic and Nonsyphilitic Individuals, Am. J. Syph. **38**:447-458 (Sept.) 1954.

120. Lucas, P. F.: The Diagnostic Value of Lymph Node Aspiration Biopsy, Postgrad. M. J. **30**:544-548 (Oct.) 1954.

121. Kardel-Vegas, F.; Kopf, A. W., and Tolmach, J. A.: Keratoderma Punctatum Syphiliticum: Report of a Case, Brit. J. Dermat. **66**:449-454 (Dec.) 1954.

122. Rajam, R. V., and Rangiah, P. N.: Early Syphilitic Hepatitis, Indian J. Ven. Dis. **20**:83-94 (July-Sept.) 1954.

123. Bradford, J. K.: Pulmonary Syphilis, Ochsner Clin. Rep. **1**:40-45 (Jan.) 1955.

124. Castigliano, S. G.: Pseudotumoral Syndrome: Syphiloma of the Pancreas; Fourteen Year Control, Am. J. Roentgenol. **72**:45-50 (July) 1954.

125. Rosahn, P. D.: The Occurrence of Malignant Disease in Syphilitic Individuals, Am. J. Syph. **38**:413-421 (Sept.) 1954.

126. Jordan, F. L., and Schlesinger, F. G.: Studies on the Destruction of Red Blood Cells in Paroxysmal Cold Hemoglobinuria of the Donath-Landsteiner (Syphilitic) Type, Acta med. scandinav. **151**:107-116 (Feb. 23) 1955.

127. Thomas, E. W.; Shafer, J. K.; Zwally, M. R., and Price, E. V.: Factors Leading to Development of Late Manifestations of Syphilis, Am. J. Syph. **38**:531-553 (Nov.) 1954.

128. Whiteman, N. C., and Mihaly, J. P.: Aortic Aneurysm: Analysis of Statistics from the Harlem Hospital 1932-1952, Harlem Hosp. Bull. **6**:145-150 (March) 1954.

129. Katz, F., and Scott, A. I.: Follow-Up Studies in Cardiovascular Syphilis, Canad. M. A. J. **72**:274-279 (Feb. 15) 1955.

130. Brandfonbrener, M., and Eisenberg, H.: The Aortic Electrokymogram in Normal Subjects and Patients with Syphilitic Aortic Insufficiency, Am. Heart J. **48**:54-65 (July) 1954.

131. Blakemore, A. H., and Voorhees, A. B., Jr.: Aneurysm of the Aorta: A Review of 365 Cases, Angiology **5**:209-231 (June) 1954.

132. Cranley, J. J.; Herrmann, L. G., and Preuninger, R. M.: Natural History of Aneurysms of the Aorta, A. M. A. Arch. Surg. **69**:185-197 (Aug.) 1954.

133. Levine, G.; Burke, E. N., and Arnois, D. C.: Roentgenologic Diagnosis of Aneurysm of the Thoracic Aorta with Particular Reference to Study in the Right Posterior Oblique Position, Am. J. Roentgenol. **72**:1004-1016 (Dec.) 1954.

134. Horne, G. O.: Dissecting Aneurysm of the Aorta: Differential Diagnosis from Syphilis, Brit. J. Ven. Dis. **30**:88-97 (June) 1954.

135. Brink, A. J., and Barnard, P. J.: Syphilitic Aneurysm of the Left Ventricle of the Heart with Calcification and Ossification, South African M. J. **28**:476-480 (June 5) 1954.

136. King, A. B., and Beirne, M.: Syphilitic Gummatous Meningitis Involving the Gasserian Ganglion, Guthrie Clin. Bull. **24**:142-146 (Jan.) 1955.

137. Antes, E. H.: Charcot Joint in Diabetes Mellitus, J. A. M. A. **156**:602-603 (Oct. 9) 1954.

138. White, N. M.: Depressive Reaction Masking Neurosyphilis, Delaware M. J. **26**:202-204 (Aug.) 1954.

139. Currier, R. D.; DeJong, R. N., and Bole, G. G.: Pulseless Disease: Central Nervous System Manifestations, Neurology **4**:818-830 (Nov.) 1954.

140. Saslaw, S., and Sakol, M.: Acute Meningovascular Syphilis During the Poliomyelitis Season, Ohio M. J. **50**:665-667 (July) 1954.

141. Steiner, G.: Comparison of General Paresis and Mutiple Sclerosis in Regard to the Etiological Agent, J. Neuropath & Exper. Neurol. **13**:492-496 (July) 1954.

142. Rao, S.: Neurosyphilis: The Common Types in Hyderabad, J. Indian M. A. **24**:48-51 (Oct. 16) 1954.

143. Donohue, J. F., and Remein, Q. R.: Long-Term Trend and Economic Factors of Paresis in the United States, Pub. Health Rep. **69**:758-765 (Aug.) 1954.

144. We Are All Concerned, Arizona Pub. Health News **49**:3-7 (Jan.) 1955.

145. Houser, J. L., and Leland, S. J.: Idaho Studies Its VD Control Program, J. Social Hyg. **40**:296-300 (Nov.) 1954.

146. Dunlop, E. M. C., and Zwink, F. B.: Incidence of Corneal Changes in Congenital Syphilis, Brit. J. Ven. Dis. **30**:201-209 (Dec.) 1954.

147. Kissel, P.; Arnould, G.; Hartemann, P., and Dureaux, J.: Signe d'Argyll-Robertson unilatéral au course d'un syndrome neuroanémique Biermeirien, Rev. méd. Nancy **79**:303-307 (May 1-15) 1954.

148. Naquin, H. A.: Argyll Robertson Pupil Following Herpes Zoster Ophthalmicus: With Remarks on the Efferent Pupillary Pathways, Am. J. Ophth. **38**:23-33 (July) 1954.

149. Apter, J. T.: The Significance of the Unilateral Argyll Robertson Pupil: I. A Report of 13 Cases, Am. J. Ophth. **38**:34-43 (July) 1954.

150. Apter, J. T.: The Significance of the Unilateral Argyll Robertson Pupil, Am. J. Ophth. **38**: 209-222 (Aug.) 1954.

151 Vogt, E.: Selective Filtration of Syphilitic Reagins Through the Placenta, Acta pædiat. **43**: 247-251 (May) 1954.

152. Hallgren, B., and Hollstrom, E.: Congenital Syphilis: A Followup Study with Reference to Mental Abnormalities, Acta psychiat. et neurol. scandinav., Supp. 93, pp. 1-81, 1954.

153. Thomas, E. W.: The Management of Syphilis, Clin. Med. **61**:611-616 (Aug.) 1954.

154. Simons, R. D. G. P.: What Are the Prospects of Modern Antisyphilitic Therapy? Its Critical Period; Divergent Opinions Concerning Antibiotic Therapy; Observations on 500 Patients, Nederl. tijdschr. geneesk. **98**:3295-3301 (Nov. 13) 1954.

155. Symposium on Penicillin, Foreign Letters (England), J. A. M. A. **157**:940 (March 12) 1955.

156. Rajam, R. V., and Rangiah, P. N.: Treatment-Resistant Syphilis: Short Review and Report of a Case, Brit. J. Ven. Dis. **31**:25-29 (March) 1955.

157. Idsøe, O., and Guthe, T.: Penicillin Treatment of Treponematoses with Special Reference to PAM in Syphilis, Tidsskr. norske lægefor. **4**:275-289 (April 15) 1954.

158. Kolmer, J. A.: Chemotherapy of Spirochetal Infections, Ann. New York Acad. Sc. **59**:214-226 (Sept. 23) 1954.

159. Rein, C. R.; Buckwalter, F. H.; Mann, C. H.; Landy, S. E., and Flax, S.: Time-Dosage Relationship in the Treatment of Treponemal Diseases with a New Combination of 3 Penicillin Salts, Am. J. Syph. **38**:408-412 (Sept.) 1954.

160. Kanee, B., and Nelson, A. J.: Challenging Trend in Venereal Disease Control. Am. J. Syph. **38**:354-360 (Sept.) 1954.

161. Willcox, R. R.; Guthe, T.; Idsøe, O., and Reynolds, F. W.: A Study of Current Treatment Practices in Early Syphilis Throughout the World, Am. J. Syph. **38**:388-396 (Sept.) 1954.

162. Willcox, R. R.: Treatment of Early Syphilis, Med. Illus. **8**:663-669 (Oct.) 1954.

163. Cutler, J. C.; Olansky, S., and Price, E. V.: Treatment of Early Syphilis, A. M. A. Arch. Dermat. **71**:239-244 (Feb.) 1955.

164. Carteaud, A. J. P.: L'Activite des antibiotiques autres que la penicilline dans la syphilis récente, Thesis, Paris, 1954.

165. Buckinger, R. H.; Hookings C. E. and Garson W.: A Preliminary Report on the Effect of Carbomycin in Early Syphilis, Antibiotic Med. **1**: 100-103 (Feb.) 1955.

166. Mazzini, M. A., and Blasi, A. A.: Treatment of Early Syphilis with Chloromycetin, Am. J. Syph. **38**:341-344 (July) 1954.

167. Willcox, R. R.: Treatment of Late Syphilis in Seamen, M. Press **232**:426-429 (Nov. 10) 1954.

168. Johnson, S. A. M.; Jansen, G. T., and Shapiro, H. H.: Cardiovascular System Syphilis, A. M. A. Arch. Dermat. & Syph. **70**:799-802 (Dec.) 1954.

169. Edeiken, J., and Beerman, H.: Penicillin Treatment of Cardiovascular Syphilis, M. Clin. North America **38**:1757-1765 (Nov.) 1954.

170. DeBakey, M. E.; Cooley, D. A., and Creech, O., Jr.: Treatment of Aneurysms and Occlusive Disease of the Aorta by Resection, J. A. M. A. **157**:203-208 (Jan. 15) 1955.

171. Dubost, C., and Dubost, C.: Resection of Aneurysms of the Aorta, Angiology **5**:260-281 (June) 1954.

172. Rausch, N. G.: Spinal Fluid Evaluation in Neurosyphilis, New York J. Med. **54**:2708-2710 (Oct. 1) 1954.

173. Gianascol, A. J.; Weickhardt, G. D., and Neumann, M. A.: Penicillin Treatment of General Paresis: A Clinicoanatomic Study, Am. J. Syph. **38**:251-259 (July) 1954.

174. Timberlake, W. H.: Review of Psychiatric Progress in 1954: Neurosyphilis, Am. J. Psychiat. **3**:524-527 (Jan.) 1955.

175. Horne, G. O.: Topical Cortisone in Syphilitic Interstitial Keratitis: Review of 23 Cases (29 Eyes), Brit. J. Ven. Dis. **31**:9-24 (March) 1955.

176. Horne, G. O.: Topical Cortisone in the Treatment of Syphilitic Interstitial Keratitis: Preliminary Report of 20 Cases (26 Eyes), Brit. J. Ophth. **38**:669-672 (Nov.) 1954.

177. North, D. D.: The Treatment of Interstitial Keratitis, Brit. M. J. **2**:7 (July 3) 1954.

178. Hahn, R. D.: Zellmann, H. E.; Naquin, H.; Cross, E. S., and Marcus, D. M.: Some Observations on the Course of Treated Syphilitic Primary Optic Atrophy, J. Chron. Dis. **1**:601-621 (June) 1955.

179. Klauder, J. V., and Gross, B. A.: Results of Penicillin, Cortisone, and Nonpenicillin Treatment of Syphilitic Optic Atrophy, with Report of Clinical Observations, Am. J. Syph. **38**:270-287 (July) 1954.

180. Morton, R. S.: The Prevention of Congenital Syphilis, Brit. M. J. **1**:1470-1472 (June 26) 1954.

181. Smith, C. A.; Gleeson, G. A., and Jenkins, K. H.: Penicillin Treatment for Early Congenital Syphilis, Arch. Pediat. **72**:12-25 (Jan.) 1955.

182. Bos, S. E.; de Bruijne, J. I., and vanWermeskerken, W. M.: Late Observations on Infants with Congenital Syphilis Treated Exclusively with Penicillin, Nederl. tijdschr. geneesk. **98**:2060-2064 (July 24) 1954.

183. Wattiez, P.: La reaction d'Herxheimer dans le traitement de la syphilis congénitale par la penicilline, Acta pædiat. belg. **8**:43-48, 1954.

184. Enkvist, O.: Fever in Early Congenital Syphilis, Acta dermat.-venereol. **34**:330-340, 1954.

185. Editorial, Brit. J. Ven. Dis. **30**:67 (June) 1954.

186. Rosenthal, A.: Eight Fatal Anaphylactic Reactions to Penicillin, New York J. Med. **54**:1485-1487 (May 15) 1954.

187. Etter, R. L., and Merryman, G.: Anaphylactic Shock and Death Due to Penicillin, Ann. Allergy **12**:453-454 (July-Aug.) 1954.

188. Morrisset, L. M.: Penicillin Anaphylaxis: Case Report, Texas J. Med. **51**:77-78 (Feb.) 1955.

189. Eisenstadter, D., and Hussar, A. E.: Severe Anaphylactic Reaction from Oral Penicillin, Am. Pract. & Digest Treat. **5**:783-785 (Oct.) 1954.

190. Bell, R. C.; Rannie, I., and Wynne, N. A.: Adverse Reactions to Procaine Penicillin in Cats and Man, Lancet **2**:62-66 (July 10) 1954.

191. Paull, A. M.: Occurrence of the "L. E." Phenomenon in a Patient with a Severe Penicillin Reaction, New England J. Med. **252**:128-129 (Jan. 27) 1955.

192. Huber, G.: Penicillinschäden des Zenmittelallergose und Herxheimersche Reaktion, Deutsche Ztschr. Nervenh. **171**:460-473, 1954.

193. Laird, S. M.: Yaws in Manchester, Brit. J. Ven. Dis. **31**:30-32 (March) 1955.

194. Treponematoses Control in Thailand, Chron. World Health Organ. **8**:349-353 (Dec.) 1954.

195. Treponematoses in Gambia: Preliminary Communication, Medical Memoranda, Brit. M. J. **2**:1270-1271 (Nov. 27) 1954.

196. Rein, C. R.: Bacteriologic and Serologic Aspects of Pinta, Am. J. Syph. **38**:336-340 (July) 1954.

197. Manson-Bahr, P. E. C.: Fijian Syphilis, Tr. Roy. Soc. Trop. Med. & Hyg. **48**:242-246 (May) 1954.

198. Willcox, R. R.: Njovera, Central African J. Med. **9**:30-33 (Jan.) 1955.

199. Hill, M., and Mugge, R.: Syphilis Prevalence as Related to Social Factors in a Negro Subcommunity, Am. J. Syph. **38**:583-592 (Nov.) 1954.

200. Buckinger, R.: Modern Trends in Syphilis Treatment and Control, Memphis M. J. **29**:98-102 (July) 1954.

201. Bell, E. T.: Decline in Mortality from Syphilis in Minnesota, A. M. A. Arch. Path. **59**:259-260 (Feb.) 1955.

202. Vought, R. L.; de Mello, L., and Ames, W. R.: The Decline and Fall of Syphilis in New York State 1936-1953: II. Early Congenital Syphilis, Am. J. Syph. **38**:361-370 (Sept.) 1954.

203. Downward Trend in Venereal Diseases is Leveling Off in California, California's Health **12**: 60-61 (Oct. 15) 1954.

204. Quintero, E.: Epidemic Syphilis in Puerto Rico and the Present Epidemiologic Approach, Bol. Asoc. méd. Puerto Rico **46**:302-305 (June) 1954.

205. Engel, C.: The Present Status of Syphilis in Australia: A Clinical, Not Strictly Satisfactory, Study, M. J. Australia **2**:286-289 (Aug. 21) 1954.

206. Eliot, T. D.: Norway Conquers Venereal Diseases, Brit. J. Ven. Dis. **31**:2-8 (March) 1955.

207. Laird, M.: Prevalence of Syphilis in Ceylon: Report Based on the Results of Serological Surveys Made by the World Health Organization of V. D. Control Team, 1951-1952, Brit. J. Ven. Dis. **30**:98-100 (June) 1954.

208. Katzenellenbogen, I.: Syphilis in Palestine: A Study Extending over 30 Years (1924-1954), Harefuah **47**:144-146 (Oct. 1) 1954.

209. Detection of Sources of Syphilis, Foreign Letters (Denmark), J. A. M. A. **156**:556 (Oct. 2) 1954.

210. Donohue, J. F.; Gleeson, G. A.; Jerkins, K. H., and Price, E. V.: Venereal Disease Among Teen Agers, STS Relationship to Juvenile Delinquency, Pub. Health Rep. **70**:453-461 (May) 1955.

211. Pinckney, E. R.: Role of the Dentist in the Detection of Nondental Disease, J. Am. Dent. A. **50**:185-190 (Feb.) 1955.

212. Kavinoky, N. R.: Premarital Medical Examinations, J. A. M. A. **156**:692-695 (Oct. 16) 1954.

213. Halse, L. M., and Liberti, D. V.: Prenatal Health Examination Legislation: History and Analysis, Pub. Health Rep. **69**:105-110 (Feb) 1954.

214. Graham, R. M.: Can Pre-Employment Serologic Tests for Syphilis Be Justified? Indust. Med. **24**:73-74 (Feb.) 1955.

215. Downing, J. G.: Syphilis in Industry J. A. M. A. **158**:468-472 (June 11) 1955.

216. Shepard, A. C., and Page, W. J., Jr.: Venereal Disease in Agricultural Migrants—New Jersey, 1953, Pub. Health Rep. **69**:831-835 (Sept.) 1954.

217. Watson, K. G.: Medical Aspects of Mid-20th Century Migration as Gleaned from Migrant Selection in Greece, with Particular Reference to Australia and the Selection of 2500 Greek-Australian Rural Workers, M. J. Australia **2**:203-207 (Aug. 7) 1954.

218. Stuart, J., and Joyce, G.: Venereal Disease Contacts of Merchant Seamen, Pub. Health Rep. **69**:1197-1199 (Dec.) 1954.

219. Preliminary Statistics of Navy Medicine: Fiscal Year 1954, Stat. Navy Med. **10**:3-29 (Oct.) 1954.

220. Rein, C. R.; Kostant, G. H., and Kimmelman, J. A.: Special Problems in the Diagnosis and Management of Syphilis in Military Personnel, U. S. Armed Forces M. J. **5**:939-948 (July) 1954.

221. Lentino, W.: Medical Evaluation of a System of Legalized Prostitution, J. A. M. A. **158**:20-23 (May 7) 1955.

222. Watson, C.: Recent Changes in French Policy on Venereal Diseases and Prostitution, Brit. J. Ven. Dis. **30**:103-113 (June) 1954.

223. Schamberg, I. L.: "Operation Streetcorner," Pennsylvania M. J. **57**:1181-1182 (Dec.) 1954.

224. Schamberg, I. L.: "Operation Streetcorner," Philadelphia Med. **50**:370-371 (Nov. 5) 1954.

225. Morton, R. S.: The "Pre-Contemporary" Syphilitic Defaulter, Brit. J. Ven. Dis. **30**:198-200 (Dec.) 1954.

Case Reports

PULMONARY INFARCTION COMPLICATING MUMPS

CAPT. LEROY J. YOUNG (MC)
and
MAJOR RAY G. COWLEY (MC), U. S. Army

ALTHOUGH pulmonary infarction is comparatively common in many phases of medicine, its occurrence as a complication of mumps is apparently rare. A survey of the medical literature by the Armed Forces Medical Library revealed only two papers pertaining to pulmonary infarction associated with mumps. In 1952 Cottel and Hauser [1] reported a case of severe bilateral mumps orchitis, parotitis, and encephalitis in a 28-year-old white man, complicated by the development of two distinct pulmonary infarcts. The following year Lehmus [2] reported a case of mumps with orchitis complicated by pulmonary infarction in a 28-year-old man. It is the purpose of this report to present a case of mumps with orchitis complicated by bilateral pulmonary infarcts.

REPORT OF CASE

A 41-year-old white male sergeant was admitted to the Medical Service of a U. S. Army Hospital on Jan. 14, 1955, with a diagnosis of mumps (epidemic parotitis). Three days prior to admission he had developed fever, anorexia, and pain and swelling in the left submaxillary area. Two days prior to admission he noted headache, pain in left jaw on swallowing, and left testicular pain. On the day of admission the left testicle became markedly swollen, more painful, and very tender. At the onset of symptoms he was given two injections of penicillin at a dispensary. The patient had been in the presence of a child with mumps approximately three weeks prior to the onset of the present illness.

Past history revealed measles and chickenpox in early childhood, three episodes of pneumonia (1927, 1929, 1937) without complications, and malaria in 1936.

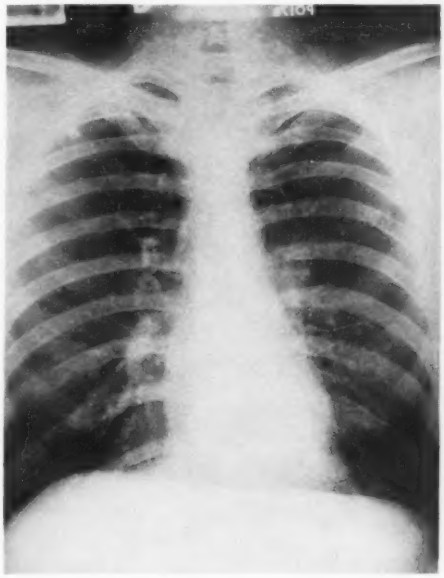
Submitted for publication July 11, 1955.

Admission physical examination revealed a well-developed middle-aged man who appeared moderately ill. B. P., 130/80. Pulse rate, 80. Temperature, 102 F. There was marked swelling of the left submaxillary gland and slight swelling of the right submaxillary gland, with tenderness and edema in both regions. The left testis was firm, warm, exquisitely tender, and enlarged to approximately three times normal size. The remainder of the physical examination was within normal limits.

Laboratory studies on admission showed the WBC count to be 8000, with the following differential count: band cells, 21%; polymorphonuclear cells, 23%; lymphocytes, 31%; eosinophiles, 3%; basophiles, 1%. Hemoglobin, 16 gm. Hematocrit value, 50%. The urine showed a trace of albumin but was otherwise normal. Mumps complement-fixation titer (third day of illness) was 1:16. Cardiolipin, negative. Chest roentgenogram and EKG were within normal limits.

The patient was placed in isolation on complete bed rest. The initial treatment consisted of scrotal support; diethylstilbestrol U. S. P. (Stilbestrol) 1 mg. q. i. d.; i. v. fluid therapy; codeine; acetylsalicylic acid, phenacetin, and caffeine, and chlor-

Figure 1



tetracycline (Aureomycin) 250 mg. q. i. d. During the first four hospital days the temperature elevation between 101 and 103.4 F persisted; the patient remained acutely ill and was increasingly anorexic and nauseated. I. v. fluids were given for 48 hours. The submaxillary gland enlargement gradually subsided, becoming nondiscernible by the fifth hospital day (eighth day of illness). Chlortetracycline was discontinued after three days because of nausea following ingestion. Diethylstilbestrol was continued for seven days. A repeat mumps complement-fixation test on the 10th day of illness revealed a titer of 1:32, which represented a significant increase. The left testicular swelling decreased over a period of two weeks, at which time the testis was soft, approximately twice normal size, and moderately tender on palpation. A minimal degree of activity was allowed during the initial two weeks of hospitalization, i. e., sitting up in bed and dangling. On the 17th day of illness (14th hospital day) the patient was permitted to walk. After two days of ambulation the patient complained of severe pain in the left chest and a mild cough. Physical examination at this time revealed a temperature of 99.4 F; pulse rate, 96, and respirations, 32. There was splinting of the left chest, with shallow respiratory movements. Diminished transmission of breath sounds was found on auscultation. The thoracic cage was tender to palpation over the area of pain. Careful initial and frequent follow-up examinations of legs by several observers failed to reveal any evidence of phlebothrombosis of thrombophlebitis. There was no external evidence of spermatic vein thrombosis. Chest x-ray taken 24 hours after onset of chest pain was interpreted as showing minimal pneumonitis, left base (Fig. 1). EKG showed no significant change from original pattern. The patient was again placed on complete bed rest, and penicillin and streptomycin therapy was instituted. Forty-eight hours after the onset of left pleuritic pain the patient complained of right-sided chest pain. Approximately 72 hours after onset of left pleuritic pain the cough became productive of grossly bloody sputum. A low-grade fever was present during the first 72 hours, and the temperature became normal thereafter. The pulse rate was slightly elevated. Repeat chest roentgenograms at this time showed bilateral pulmonary infiltrates compatible with the clinical impression of pulmonary infarction (Fig. 2). Repeat EKG was within normal limits. At this point bishydroxycoumarin (Dicumarol) therapy was started. The cough, hemoptysis, and chest pain subsided over a two-week period. Streptomycin was discontinued after 5 days, and penicillin, after 13 days. After two weeks of anticoagulant therapy the patient was permitted to walk and progressed satisfactorily. Bishydroxycoumarin was discontinued after 22 days. On discharge, after 47 days in the hospital, the patient was completely asymptomatic. The left testis was soft and atrophic, and the chest roentgenogram showed a pleural reaction with adherence of the left diaphragm to the chest wall (Fig. 3).

Figure 2

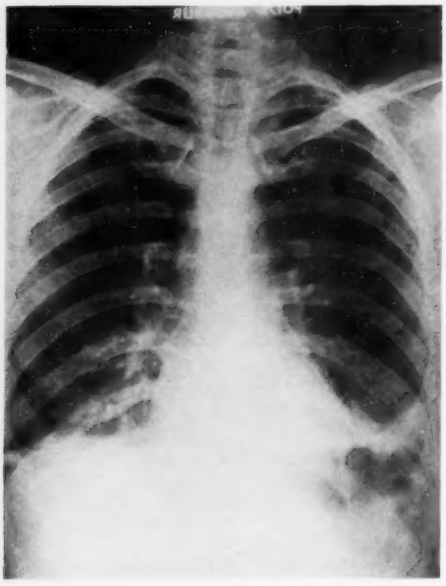
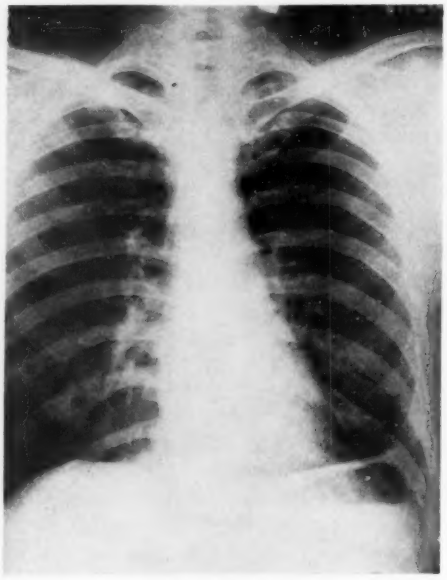


Figure 3



A follow-up examination two months later revealed no further symptoms, and chest x-ray continued to show the same findings as those in Figure 3.

COMMENT

The findings of bilateral submaxillary involvement, orchitis, a significant rise of the mumps complement-fixation titer, and the history of exposure to mumps at an appropriate time leave little doubt that this was a case of mumps, even though there was no evident parotid involvement. The clinical picture and x-ray findings are quite definitely indicative of several small pulmonary infarctions occurring over a period of approximately 48 hours. The source of the emboli producing the infarctions was not determined. The leg veins would be a logical source in a patient with a subsiding acute illness who had been confined to bed for two weeks. Reimann [3] states that, according to different observers, from 70% to 95% of the emboli come from thrombotic veins of the legs, with the remainder originating from the pelvic veins during pregnancy, puerperal sepsis, prostatitis, and from mural thrombi in the right chambers of the heart. It is well known that thrombus formation in leg veins resulting in pulmonary embolism may be entirely silent. The two previous articles on the subject of infarction complicating mumps referred to the pelvic venous plexus as a possible source. This is a possible source in this case, particularly in the face of involvement of the lower generative tract with an active inflammatory process. However, there is no concrete evidence to substantiate such a presumption.

SUMMARY

Pulmonary infarction complicating a case of mumps in an adult is presented. This is the third such case reported according to the information available to us at this time. Although the source of the emboli to the lungs could not be determined, the pelvic venous plexus is postulated as the source in view of inflammatory involvement of the lower generative tract and the complete absence of findings pointing to the veins of the legs.

REFERENCES

1. Cottel, C. E., and Hauser, M.: Pulmonary Infarction Complicating Mumps, Northwest Med. **51**:40, 1952.

2. Lehmus, H. J.: Pulmonary Infarction Complicating Mumps, Connecticut M. J. **17**:507, 1953.

3. Reimann, H. A., in Textbook of Medicine, edited by R. L. Cecil and R. F. Loeb, Ed. 8, Philadelphia, W. B. Saunders Company, 1953.

DISSEMINATED ACTINOMYCOSIS TREATED WITH TETRACYCLINE

WILLIAM J. MARTIN, M.D.
DONALD R. NICHOLS, M.D.
WILLIAM E. WELLMAN, M.D.
and
LYLE A. WEED, M.D., Rochester, Minn.

CASES in which localized actinomycosis has responded to members of the tetracycline group of compounds have been reported, but no case such as this one has been reported as far as we know, in which the actinomycosis was disseminated and seemed to respond to tetracycline.*

REPORT OF CASE

The patient was a white man, 39 years old, a supervisor in an aircraft plant. He came to the Mayo Clinic on Jan. 11, 1954, with a chief complaint of painful nodules under the skin and generously distributed throughout his body.

History.—About 1941, curettage had been done twice weekly for about four months in treatment of severe pyorrhea. From 1941 to 1948 the patient frequently had had sore throat. In the summer of 1950 he had undergone two dental extractions.

In October, 1950, several symptoms had become noteworthy. Bodily aching had been general, but the regions chiefly affected had been the thoracic portion of the spinal column, the shoulders, and the right arm. The pains had been sharp, had lasted for hours at a time, and had continued intermittently for about six months. The man had had a sensation of epigastric fullness and had belched after meals. These manifestations and intermittent fever, he said, had been attributed to infection of the urinary tract. Sedimentation of erythrocytes had been rapid.

In July, 1951, acute pericarditis had developed. Symptoms had been acute substernal pain made worse by coughing and breathing. Simultaneously, signs of right pleural effusion had developed and fluid had been aspirated, but definite diagnosis had not been made.

In the fall of the same year the man had been given oxytetracycline, 2 gm. daily for 16 days, and he had felt fairly well for about a year. The sedimentation rate of erythrocytes then dropped to 6 mm. in an hour, and in December, 1951, it was still only 8 mm. in an hour.

In June, 1952, the rectal sphincter had been cut in the course of incision of a perirectal abscess. Because of partial incontinence, the patient wore an anal pad.

In October, 1952, the superior vena cava had become thrombosed. Coincidentally, collateral veins about the thorax and neck had become apparent and great dyspnea had developed. Moreover, swelling of the face and neck had begun; this was to continue for several months. Thoracic roentgenograms, taken Dec. 10, 1952, were said to have revealed smooth, unlobed widening of the mediastinum anterior to the heart.

In June, 1953, the man had noticed that clear fluid had begun to drain rather profusely from his nose. Over the same period of time he had noticed a gradual increase in exertional dyspnea.

In July, 1953, the patient had begun to have episodes of hemoptysis, during which he would spit up as much as a cupful of bright blood. These episodes had continued intermittently until five days before his registration at the Mayo Clinic.

Also in July, 1953, administration of cortisone, 25 mg. four times daily, had begun; this was to continue for three months. After cortisone had been given, the man had noticed a painful red nodule beneath the skin of the right flank. This had been excised on Aug. 18, and the report of the pathologist had been "acute and chronic inflammation with fat necrosis." Material obtained from ulcers had given no growth on culture. Thereafter the patient had noticed, under the skin of the legs, arms, back, and scalp, numerous lumps which initially had been exquisitely tender and, usually, warm and red. To look ahead for a moment, by the time the patient came to us only one of these nodules was to have disappeared without breaking down. After the nodules had begun to appear, the patient had noticed two phenomena: there were occasional febrile episodes in the course of which the temperature had risen as high as 101 F and also swelling of the legs, especially the left, and swelling of the left arm.

Received for publication Aug. 24, 1955.

Mayo Clinic and Mayo Foundation, Section of Medicine (Drs. Martin, Nichols, and Wellman) and Section of Bacteriology (Dr. Weed). The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

* The tetracycline (Achromycin) for this study was supplied through the courtesy of Lederle Laboratories Division, American Cyanamid Company, Pearl River, N. Y.

Still in 1953, August and September, beneath the pads of the fingers and toes red swellings had developed and had ruptured spontaneously and a watery purulent material had been discharged from them. In October a physician had described areas denuded of hair around two nodules of the scalp, each of which was approximately 1 cm. in diameter; from one of these a thin purulent material had been discharged.

The patient had had much malaise which, however, had not been sufficient to prevent his working. His weight had varied considerably; at one time it had been down to 145 lb. (about 66 kg.), but for a time before we saw him it had been maintained at approximately 185 lb. (about 84 kg.).

At the time of the patient's initial examination in Rochester, on Jan. 11, 1954, he reported that he had little appetite but drank considerable fluid. He believed that 6 to 8 tablets of acetylsalicylic acid daily gave him relative comfort, although the subcutaneous nodules still caused some pain.

Examination and Treatment.—The patient was so weak that he had great difficulty undressing and dressing himself. His oral temperature was 99.4 F. He appeared chronically ill. His face and neck were puffy, probably because of the thrombosis of the superior vena cava. Collateral veins, especially those of the right side of the thorax, were much dilated, and the veins of the right side of the neck were distended. Moderate pitting edema of both feet and both legs was more marked on the left. Swelling of the left arm apparently had to do with a large indurated area in the region of the left elbow. Another such area was over the calf of the right leg.

The blood pressure was 130/70. The radial pulse rate was 120 beats per minute. Extrasystole was frequent. A systolic murmur, Grade 2, was heard best along the left sternal border in the third intercostal space, and there was gallop rhythm. Physical findings suggested fluid in the right pleural space. The patient appeared very dyspneic.

Moderate axillary lymphadenopathy was bilateral. A number of hard subcutaneous nodules were palpated. They were warm to the touch, reddish, and tender and were situated on the right wrist, left elbow, and right thigh. They varied in size from 1 cm. in diameter to the dimensions of the largest of them, 15 by 13 by 5 cm.; this largest lesion was a fluctuant mass overlying the right scapula (Fig. 1). Some of the nodules apparently had ulcerated, and a serosanguineous material was draining from them. Other lesions appeared to be healing and were covered with scaly thin scar tissue.

Because of the patient's extreme physical disability, he was hospitalized immediately. Shortly thereafter, by aspiration, abundant thick foul greenish-yellow material was obtained from one of the lesions on the dorsum of the right wrist and from the lesion over the right scapula. This material was cultured for various pathogens, including fungi. On the day after the patient's admission to hospital, he spat up approximately 100 cc. of bright red blood.

On Jan. 19, 1954, Actinomyces israeli was found in cultures of material aspirated from the right wrist, and soon in that obtained from over the right scapula and the right calf. In vitro, the organism was sensitive to the action of penicillin in amounts of 0.4 unit per milliliter and sensitive to the action of the tetracycline group of compounds in amounts of 0.39γ per milliliter. Since chlortetracycline and oxytetracycline were effective against

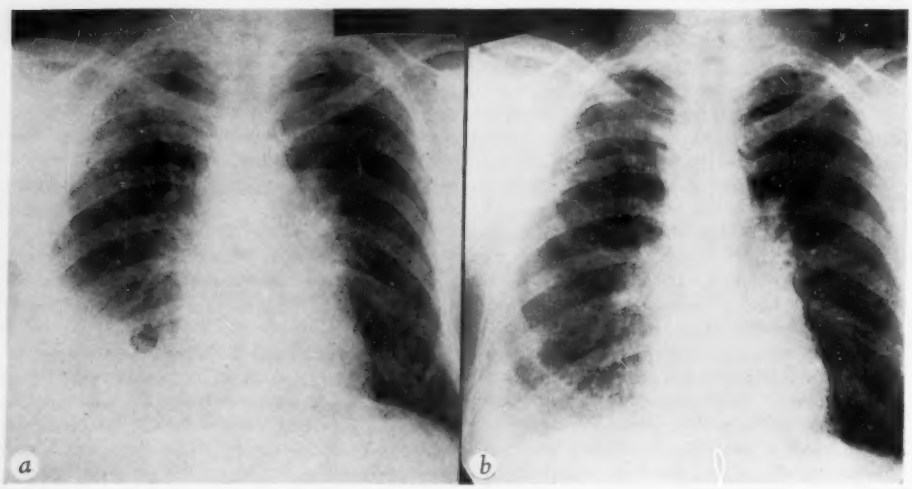
Fig. 1.—Large fluctuant abscess, right scapular region.

localized actinomycosis, we believed that their parent compound, tetracycline, would be equally effective. Thereupon, on Jan. 20, 500 mg. of tetracycline was given intravenously, and 12 hours later the dose was repeated. Then 750 mg. of the compound was given by mouth every six hours until the patient was dismissed from hospital, on Feb. 9. Subsequent treatment will be recorded in its proper place.

On the second day of intravenous therapy acute phlebitis developed on the dorsum of the left hand, where the tetracycline had been administered. This subsided in a few days. By Jan. 22 the patient was doing extremely well. His temperature became normal and remained so. He coughed less than

Fig. 2.—Lesions about (*a*) the right wrist and (*b*) the left elbow as they appeared in the middle of February, 1954. The lesions seemed to be healing and were covered with crusts and scaly thin scar tissue.

Fig. 3.—Roentgenograms of the thorax. (*a*) On Feb. 17, 1954, bilateral hilar lymphadenopathy was more conspicuous on the left; a pathologic process was widely disseminated throughout both lungs and there was fluid in the right base. (*b*) On April 5, 1955, the pulmonary lesions had resolved considerably, the hilar lymph nodes had become smaller, and there appeared to be a residuum of the process in the right upper lobe.



before, and the lesions were less tender. On Jan. 27 a lesion of the nose had cleared entirely and drainage from lesions on the left and right arms had ceased. The condition of all other lesions was improving. On Feb. 1 physical findings continued to suggest the presence of fluid in the right pleural space, and subsequently 450 cc. of clear amber fluid was aspirated through the right ninth intercostal space in the posterior lateral line.

As an outpatient, the man continued to receive tetracycline by mouth, 750 mg. every six hours.

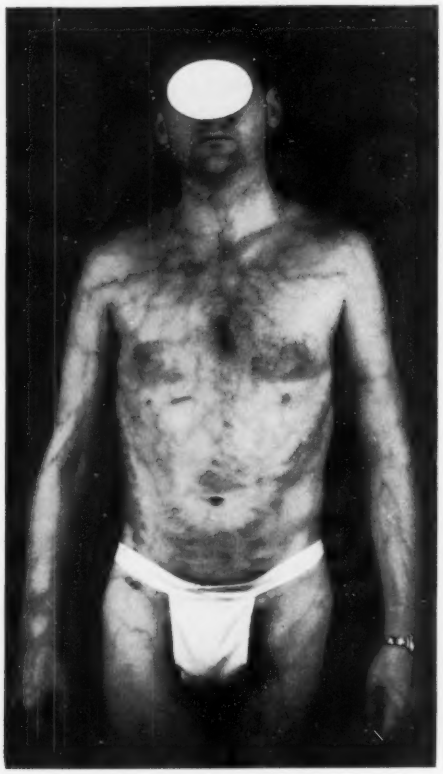


Fig. 4.—Infrared photograph taken in March, 1954, demonstrating extensive collateral venous circulation of chest and abdomen, ostensibly due to thrombosis of the superior vena cava which had occurred in October, 1952.

On Feb. 11, because he complained of mild abdominal cramps, cultures of the stool were made. From these, the normal flora and Micrococcus pyogenes were obtained. The patient continued to be afebrile; the indurated tissue over the calves had softened, and new lesions had not appeared. Also, the only draining lesion was on the left arm. Lesions of the right wrist and left elbow appeared to be improving (Fig. 2*a* and *b*). On Feb. 19 the patient complained of a pleuritic type of pain over the right portion of the thorax, and physical and roentgenographic evidence indicated an increasing amount of fluid in the right pleural space (Fig. 3*a*). Therefore, on the following day 1200 cc. of cloudy amber fluid was withdrawn through the right eighth intercostal space. On Feb. 23 the diarrhea ceased, although some micrococci continued to be found in cultures of stool. On the same day, because of moderate glossitis, a multivitamin preparation was prescribed, to be taken four times daily. Two days later the six-hour dose of the tetracycline compound was reduced to 500 mg., and on March 1, to 250 mg. On this day, an infrared photograph was made (Fig. 4). On March 6 the patient was dismissed from the clinic.

Laboratory Examination.—Urinalyses yielded normal values. In January, 1954, there was 9.6 gm. of hemoglobin per 100 cc. of blood. This gradually increased to 10.5 gm. by Feb. 18. Leucocyte counts, total and differential, remained within normal limits. The sedimentation rate on Jan. 12, 1954, was 78 mm. in an hour (Westergren method), and on Feb. 18 it had dropped to 60 mm. Values for blood urea, for blood sugar with the patient fasting, for serum bilirubin, and for blood calcium were within normal limits. On Jan. 12 retention of sulfobromophthalein (Bromsulphalein) in the serum, one hour after intravenous administration of 5 mg. of the dye per kilogram of body weight, was estimated at 12%. On Feb. 25 dye was not retained at the end of one hour after administration of the same dose. The Kline, Hinton, and Kolmer tests for syphilis gave negative results. The hematocrit value was 35%. Estimations of the total serum protein and albumin-globulin ratios were within normal limits.

Roentgenograms of the thorax initially revealed marked bilateral hilar enlargement with pulmonary infiltration. At no time did roentgenograms of the bones suggest osseous involvement. The quantity of fluid in the right pleural space varied and necessitated aspiration on the two occasions cited.

Electrocardiograms made on Jan. 12 and March 5 were within normal limits.

After Jan. 25, 1954, cultures of material obtained from the right calf, right scapular region, upper part of the left arm, left elbow, and right wrist did not yield A. israeli.

Since tetracycline had been newly introduced to the physician, its concentration in the blood and pleural fluid was studied (Table).

An electroencephalogram obtained Jan. 18 indicated the presence of generalized dysrhythmia, Grade 2, which was interpreted as indicating a diffuse process of the brain. On Feb. 26, however, an electroencephalogram gave evidence of marked improvement and suggested resolution of the process.

Follow-Up.—By Dr. Bannick: After we had dismissed the patient, on March 6, 1954, he went under the care of Dr. Edwin George Bannick, of Seattle. Dr. Bannick had the patient continue to take 750 mg. of the tetracycline compound orally every six hours until April 6, 1954, at which time he reduced the dosage to 500 mg. every six hours. This regimen continued until May 10, when the dosage was reduced further, to 250 mg. every six hours. Use of the tetracycline compound was discontinued on June 11, 1954.

An electrocardiogram ordered by Dr. Bannick on Aug. 4 was essentially normal. On Aug. 18 the erythrocyte sedimentation rate was 20 mm. in an hour. The number of erythrocytes and leucocytes in the blood and the results of urinalysis were normal.

Dr. Bannick wrote, on Aug. 28, that the patient had done remarkably well. He had steadily gained weight and strength, had worked steadily, and made no complaints. All lesions had healed, and there was no drainage. Roentgenograms gave evidence of minimal fluid in the right pleural space.

Dr. Bannick wrote again, saying that he had seen the patient on Feb. 16, 1955, at which time he was doing well, although he had become obese. He had been entirely asymptomatic except that on Dec. 15, 1954, he had awakened at 2:00 a. m. and had coughed up two mouthfuls of blood. Still, on Dec. 15, estimation of the erythrocyte sedimentation rate, routine studies of the blood, and urinalysis gave results that were within normal limits. Physical examination and roentgenograms of the thorax gave no evidence of change. On Feb. 14, 1955, roentgenograms of the thorax and physical examination again revealed no appreciable change, and again the routine urine and blood studies, including the sedimentation rate of the blood, all gave results within normal limits.

At Mayo Clinic: The patient returned for reexamination by us on April 5, 1955. He had gained 57 lb. (about 26 kg.) and reported that he had weighed 10 lb. (4.5 kg.) more than that until he had followed a reduction diet. He believed that the hemoptysis of the previous December had been caused by his resumption of smoking, which had revived a previous chronic cough. He had ceased smoking again, and hemoptysis had not recurred. He was no longer dyspneic.

Concentration of Tetracycline in Blood Serum and Pleural Fluid

Date, 1954	Dose, Mg.*	Interval (After Last Previous Dose) at Which Concentration Was Determined, Hr.	Concentration, γ/Ml.	Fluid Examined
Jan. 20	500†	None (immediately after)	11.4	Blood serum
	...	2	6.7	.....
Feb. 3	750	2	6.1	.....
Feb. 4	750	6	4.6	Pleural fluid
Feb. 9	750	4	10.0	.....
	750	8‡	7.2	.....
Feb. 11	750	8‡	12.5	Blood serum
Feb. 15	750	10‡	8.3	.....
	750	12‡	7.5	.....
Feb. 20	750	3	17.0	Pleural fluid
Feb. 25	500	6	11.0	Blood serum
March 1	250	3	10.0	.....

* Except on Jan. 20, and other exceptions which are explained below, doses were given by mouth, at intervals of six hours.

† Two doses only, given intravenously over a 2-hour period, with 12 hours between the two doses.

‡ This is one of the exceptions mentioned in footnote designated by asterisk. The dose which routinely would have been given six hours after the last previous dose was omitted in order to allow determination of the concentration of tetracycline after an interval longer than six hours.

Laboratory work at the time of this visit included urinalysis, results of which were normal. There was 13.7 gm. of hemoglobin per 100 cc. of blood; erythrocytes numbered 3,480,000, and leucocytes, 6000 per cubic millimeter. The sedimentation rate of erythrocytes was 10 mm. in an hour (Westergren method). Sulfobromophthalein was not retained in the serum at the end of one hour after 5 mg. per kilogram of body weight had been administered intravenously. Estimations of the concentration of blood urea and serum bilirubin were within normal limits. A thoracic roentgenogram revealed that the extensive pathologic process involving both lungs had considerably cleared up but there was either fluid or thickened pleura at the right base (Fig. 3*b*). The electrocardiogram still appeared practically

normal. An electroencephalogram obtained on April 6, 1955, seemed not to differ from one obtained on Feb. 26, 1954.

COMMENT

Until the advent of antibiotics, treatment of actinomycosis was not encouraging. Cervicofacial actinomycosis sometimes had responded well to several methods of treatment, including prolonged surgical drainage, roentgen therapy, and administration of iodides and sulfonamide compounds. However, pulmonary actinomycosis nearly always had been a progressive and fatal disease. Abdominal actinomycosis always had been serious, and the percentage of patients who recovered never had been large. Very few recoveries of women with actinomycosis of the pelvic viscera [1] ever had been reported. Disseminated actinomycosis represented a relatively hopeless situation.

In 1943, the Committee on Chemotherapeutic and Other Agents of the National Research Council [2] reported on the use of penicillin in treatment of three patients who had actinomycosis; the condition of one patient improved, and two died. In 1944, Herrell, Nichols, and Heilman [3] reported initial observations on the use of penicillin in treatment of 12 patients who had actinomycosis. Other investigators † also reported encouraging results from treatment with penicillin of patients afflicted with actinomycosis.

In 1948 one of us (Nichols) and Herrell [4] reported on 60 patients who had actinomycosis and had been treated with penicillin. The results indicated that penicillin was an effective agent against actinomycosis, its effectiveness varying somewhat with the situation of the lesion. At the Mayo Clinic, more than 90% of patients with cervicofacial actinomycosis, 40% of those with pulmonary actinomycosis, and 80% of those with abdominal and pelvic actinomycosis have recovered after treatment with penicillin alone; a dose of at least 500,000 units of penicillin daily, administered intramuscularly or intravenously for six weeks, appeared to give best results.

† References 4-9.

McVay and Sprunt [10] undertook a long-term evaluation of chlortetracyline (Aureomycin) in the treatment of actinomycosis. They concluded that the agent was effective in treatment of both localized and disseminated actinomycosis, and they described seven cases successfully treated. Five of their seven patients had been observed for more than two years after completion of treatment.

Seligman [11] noted that in all cases reviewed by him in which A. israeli had been isolated by culture, cure had resulted after administration of chlortetracycline. He further noted that surgical drainage had been unnecessary in all these cases except one, and in that case there was a hepatic actinomycotic lesion. Since he knew of no comparable results having been reported in actinomycosis with any form of treatment, Seligman believed that chlortetracycline must be regarded as the preparation of choice for treatment of the disease. He emphasized that adequate treatment was necessary if relapse was to be avoided.

Lane and Kutscher,[12] in seven proved cases of cervicofacial actinomycosis, used oxytetracycline with success. The periods of treatment ranged from two to six weeks. Our reasons for use of tetracycline have been explained in this report of our case. The patient's response seems to attest, in this isolated instance at least, to the efficacy of the agent. If the agent is as effective as to us it appeared to be against the disseminated form of actinomycosis, it should be effective against the localized form.

SUMMARY

Apparent arrest of disseminated actinomycosis was achieved in a case in which massive and prolonged treatment with tetracycline was employed. Actinomyces israeli was cultured from numerous lesions in the skin and subcutaneous tissues. Evidence of pleural and pulmonary inflammation suggested that the infection involved the respiratory tract. Thrombosis of the superior vena cava and pericarditis also occurred. Electroencephalographic changes and results of neurologic examination suggested possible intracranial

infection. One year after treatment with tetracycline all manifestations of infection had disappeared. This appears to be the first description of disseminated actinomycosis treated with tetracycline.

REFERENCES

1. Nichols, D. R., and Herrell, W. E.: Penicillin in the Treatment of Actinomycosis, J. Lab. & Clin. Med. **33**:521-525 (May) 1948.

2. Keefer, C. S.; Blake, F. G.; Marshall, E. K., Jr.; Lockwood, J. S., and Wood, W. B., Jr.: Penicillin in the Treatment of Infections: A Report of 500 Cases, J. A. M. A. **122**:1217-1224 (Aug. 28) 1943.

3. Herrell, W. E.; Nichols, D. R., and Heilman, D. H.: Penicillin: Its Usefulness, Limitations, Diffusion and Detection, with Analysis of 150 Cases in Which It Was Employed, J. A. M. A. **125**: 1003-1010 (Aug. 12) 1944.

4. Hamilton, A. J. C., and Kirkpatrick, H. J. R.: Actinomycosis Successfully Treated with Penicillin: Report of 2 Cases, Brit. M. J. **2**:728 (Nov. 24) 1945.

5. Decker, H. R.: The Treatment of Thoracic Actinomycosis by Penicillin and Sulfonamide Drugs, J. Thoracic Surg. **15**:430-440 (Dec.) 1946.

6. Poppe, J. K.: Treatment of Pulmonary Actinomycosis with a Report of 7 Arrested Cases, J. Thoracic Surg. **15**:118-126 (April) 1946.

7. Lamb, J. H.; Lain, E. S., and Jones, P. E.: Actinomycosis of the Face and Neck, J. A. M. A. **134**:351-359 (May 24) 1947.

8. Chanton, E. F.; Hollis, W. J., and Hargrove, M. D.: Actinomycosis: Report of 6 Cases Treated with Penicillin and Sulfadiazine, South. M. J. **41**: 1022-1026 (Nov.) 1948.

9. Sanford, G. E., and Barnes, R. O.: Massive Penicillin Therapy of Abdominal Actinomycosis, Surgery **25**:711-723 (May) 1949.

10. McVay, L. V., Jr., and Sprunt, D. H.: A Long-Term Evaluation of Aureomycin in the Treatment of Actinomycosis, Ann. Int. Med. **38**:955-966 (May) 1953.

11. Seligman, S. A.: Treatment of Actinomycosis with Aureomycin, Brit. M. J. **1**:1421 (June 19) 1954.

12. Lane, S. L., and Kutscher, A. H.: Oxytetracycline in the Treatment of Orocervical Facial Actinomycosis: Report of 7 Cases, J. A. M. A. **151**:986-988 (March 21) 1953.

News and Comment

ANNOUNCEMENTS

General Practice Meeting.—More than 5000 physicians will attend the Eighth Annual American Academy of General Practice Scientific Assembly, March 19-22, 1956, in the Washington, D. C., Armory.

During the four-day scientific meeting, 26 outstanding speakers will discuss subjects ranging from cardiac emergencies to primary wound repair. There will be more than 60 scientific and 250 technical exhibits. Highlights of the program include two live clinics, a symposium on obstetrics, and an address by Surgeon General Leonard Scheele. Special tours through the National Institutes of Health, Bethesda, Md., have been arranged. All sessions of the Congress and many social functions will be held in the Hotel Statler.

Course in Internal Medicine.—The University of Minnesota announces a continuation course in recent advances in internal medicine for internists, which will be held at the Center for Continuation Study Feb. 13 to 15, 1956. This year's program will deal principally with recent advances in the fields of endocrinology and metabolism, renal disease, and cardiology.

Guest speaker will be Dr. Joseph W. Jailer, Associate Professor, Department of Medicine, College of Physicians and Surgeons, Columbia University, New York, who will also give the Minnesota Pathological Society Lecture on Tuesday evening, Feb. 14. The course will be presented under the direction of Dr. C. J. Watson, Professor and Head, Department of Medicine. Lodging and meal accommodations are available at the Center for Continuation Study.

Western Society for Clinical Research.—The ninth annual meeting of the Western Society for Clinical Research will be held Jan. 27 and 28, 1956, at Carmel-by-the-Sea, Calif.

Information regarding the meeting may be obtained from Arthur J. Seaman, Secretary-Treasurer, University of Oregon Medical School, Portland 1, Oregon.

International Society of Hematology.—The time and place of the Sixth Congress of the International Society of Hematology have been changed to the Hotel Somerset, in Boston, the meetings to be held during the week of Aug. 26, 1956, that is, one week prior to the previously announced date.

Practical Bedside Cardiology Course.—On March 14 through 17, 1956, Dr. Samuel A. Levine, Clinical Professor of Medicine at Harvard Medical School, will present a course in practical bedside cardiology at the Texas Medical Center, Houston, Texas. Dr. Levine will be the first lecturer for the J. J. and Una Truitt endowed chair in cardiology at The University of Texas Postgraduate School of Medicine. The course, co-sponsored by the Baylor University College of Medicine and the Houston Heart Association, will comprise three full days of clinical teaching by Dr. Levine. The registration fee of $35.00 entitles a registrant to attend all or any part of the course. Application should be made to The University of Texas Postgraduate School of Medicine, Texas Medical Center, Houston 25.

International Symposium on Venereal Diseases.—The First International Symposium on Venereal Diseases and the Treponematoses will be held at the Statler Hotel, Washington, D. C., from May 28 through June 1, 1956, Surgeon General Leonard A. Scheele announced today. The symposium will be sponsored by the Public Health Service, U. S. Department of Health, Education, and Welfare, and the World Health Organization.

This symposium will afford opportunity for authorities in the field from all over the world to exchange ideas and information on the latest developments in research, diagnosis, treatment, and case finding of the venereal and treponemal diseases.

Dr. Clarence A. Smith, Chief of the Public Health Service Venereal Disease Program, is in charge of arrangements for the symposium, which is expected to draw over 500 specialists in the field of venereal disease and the treponematoses from many countries of the world.

Invitations are being sent to persons in many foreign countries with the cooperation of the World Health Organization, the International Union Against Venereal Disease, and the Pan American Sanitary Bureau. Hundreds of physicians, scientists, and health workers, from all of the states and territories of the United States, are expected as a result of invitations being extended through the Association of State and Territorial Health Officers, the Academy of Dermatology and Syphilology, the American Venereal Disease Association, and the American Social Hygiene Association.

The agenda for the symposium will cover such topics as Control of Venereal Diseases and the Treponematoses in Retrospect and Prospect; Reporting and Statistical Problems; Natural History of Syphilis and the Treponematoses; Experimental Syphilis and the Treponematoses; Serology and Immunology of the Treponematoses; Diagnosis, Management, and Prognosis of the Treponematoses and the Venereal Diseases; Gonorrhea, the Minor Venereal Diseases, and Nongonococcic Urethritis; Epidemiology and Control Techniques; Health Education and Public Information; Voluntary Agency Cooperation in Control Programs.

The symposium is open to all physicians, scientists, and professional health workers interested in participating. Anyone interested in submitting a paper for consideration by the Program Committee should send an abstract of his paper to Dr. C. A. Smith, Medical Director, Chief, Venereal Disease Program, Division of Special Health Services, Public Health Service, Department of Health, Education, and Welfare, Washington 25, D. C., as soon as possible. Accepted papers may be presented in person or by an alternate. All abstracts to be considered for the program must be received no later than Feb. 1, 1956.

The working languages of the symposium will be French, Spanish, and English. Arrangements are being made for simultaneous interpretation of papers in all three languages during the course of the meeting.

International Society of Geographic Pathology.—The Sixth Congress of the International Society of Geographic Pathology will be held in Paris, July or September, 1957. The subject for the conference will be "The Geographic Pathology of Peptic Ulcer." Plans call for a world-wide study of peptic ulcer, and the international committee in charge of arrangements would welcome participation by as many investigators from America as possible. Further information and questionnaire forms for the national study may be obtained from William B. Wartman, Secretary, American Section, International Society of Geographic Pathology, Northwestern University Medical School, Chicago 11.

American Goiter Association Meeting.—The 1956 meeting of the American Goiter Association will be held in the Drake Hotel, Chicago, May 3, 4, and 5, 1956. The program for the three-day meeting will consist of papers and discussions dealing with the physiology and diseases of the thyroid gland.

Residencies in Psychiatry.—The Veterans Administration Hospital, Lyons, N. J., has available residencies in psychiatry for a one- to three-year period which are fully accredited by the American Board of Psychiatry and Neurology. The training program consists of lectures, conferences, and seminars under the direction of the Department of Psychiatry, New York Medical College, and offers intensive training, both intramurally and through rotation in special hospitals and clinics in the adjacent area. There is, in addition, an extensive series of guest lecturers as well as an Annual Institute at this hospital. Training may commence at any time.

Books

EDITED BY WILLIAM B. BEAN, M.D.

BOOKS RECEIVED

Dermatologie der Mundhöhle und der Mundumgebung: Systematik, Morphologie und Grundzüge der Behandlung. By Priv. Doz. Dr. Aloys Greither. Price, $9.45. Pp. 262, with 191 illustrations. Georg Thieme, Herdweg 63, (14a) Stuttgart, Germany (agents in the U. S. A. and Canada, Intercontinental Medical Book Corp., 381 4th Ave., New York 16), 1955.

Hypnotic Suggestion: Its Role in Psychoneurotic and Psychosomatic Disorders. By S. J. Van Pelt, M.B., B.S. Price, $2.75. Pp. 95, with three illustrations. Philosophical Library, Inc., 15 E. 40th St., New York 16, 1956.

Kinships of Animals and Man. By Ann H. Morgan, Ph.D. Price, $6.75. Pp. 839, freely illustrated. McGraw-Hill Book Company, Inc., 330 W. 42nd St., New York 36, 1955.

The American Drug Index. By Charles O. Wilson, Ph.D., and Tony Everett Jones, M.S. Price, $5.00. Pp. 576. J. B. Lippincott Company, 227-231 S. Sixth St., Philadelphia 5; 2083 Guy St., Montreal, 1955.

Exogene Faktoren in der Pathogenese der Poliomyelitis. By Dr. R. Chr. Behrend. Price, $3.45. Pp. 98, with 25 tables. Georg Thieme Herdweg 63, (14a) Stuttgart (agents in the U. S. A. and Canada, Intercontinental Medical Book Corp., 381 4th Ave., New York 16), 1955.

Verhandlungen der Deutschen Gesellschaft für Kreislaufforschung: 21. Tagung zu Bad Nauheim vom 15. bis 17. April 1955. Themen: Koronarthrombose; Cor pulmonale. Edited by Prof. Dr. Rudolf Thauer. Price, DM 56. Pp. 484, with 183 illustrations. Dr. Dietrich Steinkopff Verlag, Holzhof-Allee 35, (16) Darmstadt, Germany, 1955.

Einführung in die Begutachtung innerer Krankheiten. By Prof. Dr. Med. Johannes Brinkmann and Dr. Med. Heinrich Bornemann. Price, DM 10. Pp. 204. VEB Georg Thieme, Hainstrasse 17-19, Leipzig C1, Germany, 1955.

BOOK REVIEWS

The Halogenated Hydrocarbons: Their Toxicity and Potential Dangers. By W. F. von Oettingen, M.D., Ph.D. P. H. S. Publication No. 414. Price, $2.50. Pp. 430, with 78 tables and 7 figures. U. S. Government Printing Office, Washington 25, D. C., 1955.

In a previous review (*Journal of Industrial Hygiene and Toxicology* **19**:349, 1937), the author covered the general field of the halogenated aliphatic hydrocarbons with respect to their toxicity and potential dangers. Since the publication of this review, many new halogenated hydrocarbons have been synthesized and a number of them have assumed importance in industrial, agricultural, and domestic usage.

The halogenated hydrocarbons are much more toxic than their parent hydrocarbons, and there appears to be no consistent relationship between toxicity and halogen content. Therefore, the toxicity must depend on the molecules themselves, and it becomes necessary to analyze each compound individually with respect to pharmacological activity, despite the many similarities in behavior of homologous series.

In the present work, the coverage of halogenated aliphatic hydrocarbons has been extended to include (1) halogenated aliphatic hydrocarbons (methane through hexane); (2) halogenated olefinic hydrocarbons (ethene through pentene); (3) halogenated diolefinic hydrocarbons, and (4) halogenated cyclic hydrocarbons. In the halogenated aromatic hydrocarbon series, benzene, toluene, xylene, diphenyl, and naphthalene derivatives are discussed. New compounds which are

finding use in insecticides, such as halogenated indanes, terpenes, and the aliphatic-aromatic types such as chlorophenothane (D. D. T.), are given thorough consideration.

Each compound is discussed with respect to its chemistry, physical properties, analytical procedures, investigative toxicology, and prophylactic measures and treatment in the event of poisoning resulting from toxic exposure.

The book, in general, comprises a valuable collection of chemical and toxicological information on materials which are being used widely and are potentially and actually dangerous to humans. The bibliography at the end of each section represents a much needed compilation of reference information, in compact form, which is not readily available elsewhere. However, it would seem that this book would be of greater interest to the industrial physician than to the general practitioner.

CARL A. DRAGSTEDT, M.D.

Hypertension: Humoral and Neurogenic Factors; Ciba Foundation Symposium. Edited by G. E. W. Wolstenholme, O.B.E., M.A., M.B., and Margaret P. Cameron, M.A., A.B.L.S. Price, 30s. Pp. 294. J. & A. Churchill, Ltd., 104 Gloucester Pl., London, W. 1, 1954.

This symposium on hypertension brings the subject up to date as of 1953. It includes an excellent review on the neurohormonal control of blood vessels, by Page; reflex regulation of blood pressure, by Heymans; chemical diagnosis of pheochromocytoma, by Goldenberg and von Euler; unusual clinical features of hypertensive disease, by Perera and Peart; pathogenesis of experimental hypertension, by Grollman, Govaerts, Floyer, and others; the pharmacology of ganglion blocking agents, by Paton; studies on electrolyte and water distribution in experimental hypertension, by Braun-Menendez and Ledingham, and other interesting experimental and clinical approaches to hypertension. Perhaps the most impressive work discussed at this Symposium is the experimental evidence for the extrarenal pressor mechanism in Goldblatt hypertension and nephrectomized animals.

The volume is well edited, very readable, and full of thought-provoking discussion. It is a superb product of a well-organized Symposium.

LOUIS LEITER, M.D.

Gestation. By Louis B. Flexner, M.D. $5.00. Pp. 238, with 96 illustrations. Josiah Macy Jr., Foundation, 16 W. 46th St., New York 36, 1955.

This book represents the transactions of the first conference on gestation sponsored by the Josiah Macy Jr., Foundation. The members of this conference were anatomists, biochemists, and physiologists, with the exceptions of two obstetricians. The subjects of the conference were the functional role of the placenta, problems of sugar transport in the placenta of the ungulate, and the comparative anatomy and histology of the placental barrier. The book is a superb contribution to basic knowledge on these subjects. The photographs and their reproductions are beautiful. The text is informally edited so that the "give and take" of the discussers is well preserved. This makes for reader interest.

Anyone who has or should have interest in fundamentals having to do with gestation should own a copy of this book.

RONALD R. GREENE, M.D.

Hematology. By Cyrus C. Sturgis, M.D. Second edition. Price, $19.50. Pp. 1222. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1955.

This is a revision of the book published in 1948. Consistent with the many new developments in the field of hematology, the size of this volume has increased from 915 to 1223 pages. The text is organized in the same style as the first edition, in which the author sets forth an interesting historical account of each major subject before going into the etiology, pathology, signs and symptoms, and treatment. As in the previous edition, interesting representative cases from the experience of the author, and others, are described. Despite the very extensive bibliography to which the author refers, he given his own evaluation of the importance of the various signs and symptoms and his own opinion with respect to treatment. Certain points of view, such as the author's disapproval of splenectomy in cases of hypersplenism secondary to lymphoma will meet with some disagreement. There is no doubt, however, that the views set forth are those of an experienced and astute clinician.

Despite the efforts at revision of this work, it omits some of the most exciting and significant developments in the field of hematology. The hemoglobinopathies are scarcely alluded to, and

the significance of this development is not properly treated, granted that this field has expanded with such extraordinary rapidity that it would be impossible to print a thoroughly up-to-date chapter at the present time. Sicklemia and leptocytosis are discussed in the classical manner, and genetic patterns are reviewed at length but are not correlated with the hemoglobinopathies, which are the very crux of the problems of the pathogenesis and inheritance of these syndromes.

The discussion of erythroblastosis fetalis is rather limited, and the indications which are cited for exchange transfusions are now outdated. Similarly, the discussions of plasma protein fractionation, red cell preservation, and plasma substitutes are not as up-to-date as one should anticipate in a new edition.

The subject of blood coagulation is an involved and controversial one at the present time, and we should not be over-critical of any attempt to give fair and comprehensive coverage of the subject. However, the average reader would likely find a shorter, better organized chapter more instructive and less confusing, even though less comprehensive.

This book has the virtues cited above and will be interesting reading from the standpoint of historical discussion and bibliography and the author's personal experiences. However, it leaves something to be desired as an up-to-date reference for the practitioner or student.

Adrenal Function in Infants and Children: 13th M & R Pediatric Research Conference. Price, not given. Pp. 102. M & R Laboratories, Columbus 16, Ohio, 1955.

The meetings of the established scientific societies have become so large that free and fearless exchange of ideas has become stifled. The opportunity for an intimate exchange of current ideas and information by investigators in a particular field is now being met by special conferences such as the Gordon Research Conference, the Josiah Macy Foundation Conferences, and the M & R Pediatric Research Conference. These conferences aim to bring together the active investigators in a field under circumstances which permit a relaxed and thorough consideration of the hypothesis, methodology, and the current status of the knowledge in the field of their investigations. Another advantage of these conferences is that the participants are invited to make presentations because of their qualifications, so that the programs may be arranged for complete coverage and as they are not dependent upon the chance presentation of papers to be incorporated into a diffuse program, such as is the lot of the established scientific societies.

Furthermore, ample time may be allowed for a full presentation of the investigators' material rather than brief ten-minute, overly condensed and hurried presentations characteristic of many scientific meetings.

The 13th M & R Pediatric Research Conference was a symposium on adrenal function in infants and children, held under the auspices of the Department of Pediatrics of the State University of New York at Syracuse, under the chairmanship of Dr. Lytt I. Gardner. Nearly every aspect of adrenal function as it pertains to the problems of infants and children was covered by a distinguished list of participants. The material included in the well-prepared summary of the conference is of great interest and importance to those interested in the function of the adrenal gland. The psychological aspects of the management of hermaphroditism and the genetics of adrenal hyperplasia are topics worthy of special mention.

The Prevention of Disease in Everyday Practice. By Isadore Givner, M.D., and Maurice Bruger, M.D. Price, $20.00. Pp. 964, with 50 illustrations, The C. V. Mosby Company, 3207 Washington Blvd., St. Louis, 1955.

This book of approximately 1000 pages is divided into 37 chapters, each on prevention in some phase of medicine, for example, preventive hematology, preventive cardiology, preventive psychiatry, preventive obstetrics, preventive proctology, etc. Each section is from the pen of a different author; all are well written and authoritative. Whether the idea of the book is a sound one I will not attempt to decide. Actually, as one can not work in a vacuum, a good deal of space is devoted to setting the stage for the remarks on the purely preventive aspects of disease, and the question is whether it is wise to try to separate prevention too sharply from other considerations. Indeed, I have an uneasy feeling that some of this could be said as well in good general textbooks. However, there is much of value between these covers and no doubt doctors will find the book of value to them.

ARTHUR L. BLOOMFIELD, M.D.

Doctor and Patient. By Desmond O'Neill, M.D., M.R.C.P. Price, $5.00. Pp. 197. J. B. Lippincott Company, 227-231 S. Sixth St., Philadelphia 5, 1955.

The title "Doctor and Patient" is an arresting one. In our day of self-conscious physicians made slightly paranoid by carping laymen we do well to attend strictly to anyone who may give us a clearer insight into the perplexing relationship of physicians and patients. I have before me on my desk three books entitled "Doctor and Patient," the first by S. Weir Mitchell, published in 1887. In it are a series of essays chiefly directed at the layman attempting to explain some of Mitchell's philosophy about certain aspects of illness, notably the psychoneurotic illness which he found in so many women patients. Titles of his essays are "The Physician," "Convalescence," "Pain and Its Consequence," "The Moral Management of Sick or Invalid Children," "Nervousness and Its Influence on Character," and "Outdoor and Camp Life for Women." Weir Mitchell, though distinguished as a neurologist, is perhaps best remembered for introducing the famous rest cure. He was memorable in his day also as a novelist and writer of skill and perception. He played a very important part in emphasizing the role of emotional factors in psychoneurosis, which often went masquerading under various mistaken diagnoses and misinterpreted labels. No doubt his sometimes fabulous and successful therapy was influenced by his majestic figure, his impressive presence, and his strong and stern personality. While he may not have bullied women into getting well, the story is told that one of his patients, a dowager with myriad symptoms and multitudinous complaints, declared herself completely unable to move from bed but was cured when she was flushed unceremoneously. Doctor Mitchell not only threatened to take his clothes off and get in bed with her but gave evidence of starting to carry out his threat.

Another "Doctor and Patient" volume is that of Francis Peabody, published in 1930 and containing four essays, "The Public and the General Practitioner," "The Care of the Patient," "The Physician and the Laboratory," and "The Soul of the Clinic." This little book of less than 100 pages contains, in beautiful simplicity, one of the truly wise statements of medical philosophy. It is focused on physicians as they were moving into the laboratory age of modern scientific medicine. The dangers of the mechanization of medicine, the loss of the patient in a flying circus of laboratory tests, the difficulties of combining a career in teaching, research, and practice are all set forth. If physicians today read no other book they would all be better for reading Peabody's small volume not once but every year.

A recent arrival on the scene, Desmond O'Neill's "Doctor and Patient" exemplifies another trend which might have been foreseen from a perceptive view of the advances Weir Mitchell helped introduce and the wise forecasting of Francis Peabody.

One of the curious phenomena of contemporary medicine has been the rediscovery of the patient by the physician whose training in laboratory medicine as a scientist has at times paralleled his lack of clinical experience. The first foray into clinical medicine after an apprenticeship in the laboratory finds him rediscovering what the good physician has known all along —that the patient is a person. This he did so naively that he felt it to be important to build up the whole new subspecialty of psychosomatic medicine. There has been an enormous amount of work, some good, some bad, much indifferent, in trying to evaluate the role which emotions may play as precipitators, causes, accelerators, or aggravators of disease. The great difficulty has been that while one can measure blood pressure with an instrument and get an unlimited amount of data the emotions cannot be so readily weighed in the balance, nor can the effect of emotions which operated in the past be measured in terms of results which influence the present. The profound difficulty of setting up clinical controls has made this field of investigation particularly prone to the errors of *post hoc, ergo propter hoc* reasoning. At the same time it has been bewildering for well-trained clinicians, sympathetic with patients, to see announced as new discoveries many facts which have long been solidly established in the corpus of the arts of medicine. Despite these difficulties, the growing awareness by physicians of the need for true and warm understanding of patients highlights the fact that scientific medicine is not enough. It hardly needs to be stated that without scientific medicine one lapses into clinical self-deception or quackery. The great difficulty of psychosomatic medicine has been that of generalizing from somewhat inadequate data. O'Neill's book, with its great emphasis on stress, makes the experienced clinician a little embarrassed because so much of what is stated is so obvious. The notion that there is an abstract state of stress which prevails widely in a great many circumstances is perhaps given too much dignity. After all, a certain amount is already known about life. This book therefore will serve as a useful introduction to very junior students, but I doubt that it will add much to

the knowledge or usefulness of a physician who is as much five years out of medical school, provided he has normal wits and sees sick people perceptively. Unfortunately little is done in this book to dispel the widely prevailing notion that stress, because associated with disease, is harmful. Life without stress is inconceivable. The dangerous notions that people need to be protected from stress, that they need to make their decisions without reference to others in the world about them, are the source of much anguish and confusion today. The welfare state, the something-for-nothing, the solution of just one individual's problems with no reference to the rest of the people concerned, all reemphasize the point that we need to teach patients how to meet stress rather than to remove stress from them and let them relapse back into a pleasant, spineless sort of an ameboid jelly.

WILLIAM B. BEAN, M.D.

Talking with Patients. By Brian Bird, M.D. Price, $3.00. Pp. 154. J. B. Lippincott Company, 227-231 S. Sixth St., Philadelphia 5; 2083 Guy St., Montreal, 1955.

I confess I opened this book, "Talking with Patients," with much misgiving because so many books of this kind treat the reader as though he were intellectually on the level of a high-grade moron and make resounding pontifications about the obvious. This is no such book. First, it separates patients into two groups, children and adults, and further divides children by ages, pointing out the remarkable language and speech differences that children of different ages exhibit, particularly in terms of their reactions and responses to the inquiries of physicians. Perhaps the theme of this book is best stated by the author who says "Any patient who comes to a doctor, for whatever reason, deserves to be looked at with the broadest kind of vision. One must place all his sense organs at the disposal of the patient and must set his mind ready to receive the telltale messages that emanate in so many forms from the patient." Samples from the wide spectrum of patients who seek out the doctor are described and discussed. In very simple and straightforward style, the particular hazards and pitfalls in obtaining the history and the importance of the physician's reactions are described perceptively and in such terms that even physicians who are disturbed by the very thought of psychiatrists will profit greatly from a careful study of the book. Much wisdom is distilled into small compass. This is the kind of book that can be understood by students of medicine as undergraduates, as interns, as residents, or as practicing physicians in all specialties and at all ages. They would all be better for a careful study of it.

WILLIAM B. BEAN, M.D.

Communicable Diseases. By Franklin H. Top, M.D. Price, $18.00. Pp. 1208, with 115 illustrations. The C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, 1955.

In this third edition of "Communicable Diseases," the content has been enlarged, the number of collaborating authorities has been increased, and five new chapters have been added. Among the latter, those on sulfonamides and antibiotics, dealing entirely with therapeutic agents, are informative and valuable additions. The chapters on virus hepatitis and primary atypical or virus pneumonia have been entirely rewritten in the light of the newer knowledge of these diseases. The hemolytic streptococcal infections are presented in detail, with specific treatment, and their important relation to rheumatic fever and control of the same are discussed.

On the basis of the present concept of immunity in influenza, types A and B are considered as two distinct diseases. The chapter on poliomyelitis is well written and includes the Sister Kenny concept and treatment, protective vaccination, and physical therapy treatment.

Preventive medicine is given a wider application in connection with the practice of medicine. The complete description of symptoms, amplified greatly by colored illustrations, with specific and other therapy of the different communicable diseases, offers a valuable guide and reference, particularly for the internist, pediatrician, and general physician.

Nutrition Practices: A Guide for Public Health Administrators. By several authors. Price, $1.00. Pp. 72. American Public Health Association, Inc., 1790 Broadway, New York 19, 1955.

"Nutrition Practices" is an authoritative guide planned as an aid to administrators of public health departments. Its purpose is to assist them to incorporate adequate nutrition service into the public health program. Suggestions are given for determining the need and opportunities for nutrition education in the community; integrating nutrition into such other units of the health department as maternal and child health, geriatrics, and tuberculosis; and evaluating the effectiveness of the program.

The guide was prepared by a committee of nutrition researchers and teachers, consultants, and state and local health administrators under the chairmanship of Dr. Daniel Bergsma, New Jersey State Health Commissioner.

Cough Syncope. By Vincent J. Derbes, M.D., and Andrew Kerr, Jr., M.D. Price, $4.75. Pp. 182, with illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1955.

Cough syncope is a relatively uncommon but by no means rare reaction which occurs in association with coughing. Hitherto it has been largely the private property of European physicians. Only recently has there been much interest in it in America. Derbes and Kerr set forth in scholarly fashion and delightful style the historic background, the vast clinical confusion, the multiplex theories used to explain the phenomenon, and the few and frequently discordant physiologic studies devoted to cough syncope. From their thoughtful study a clinical pattern emerges of a robust middle-aged Rabelaisian character, given lavishly to eat and drink, raucous in mirth and merriment, exaggerating even in coughing. Beyond the fact that such a person has a particular liability to knocking himself out with cough syncope which he tends to shrug off as a mere nothing we have had very little to go on. That little they have gathered together skillfully, indicating specially the areas where more study is needed.

It is very helpful to have both direct quotations from many different foreign languages and the translation directly following. Among the other delightful and remarkable quotations is one from Jackson and Jackson, who repeat several times over the notion of laryngeal icterus as though jaundice of the larynx rather than a spasm (or ictus) of the larynx was on their mind. The book is written in a pleasing style, is easy to read, and gives evidence of painstaking care in preparation. The style, which has a good deal of the gusto of the typical victim of cough syncope, has one or two syncopal spells itself, as on page 64, where the word "counterpart" is used where the word "opposite" is meant; and on page 79 is a statement that "theory must have an influence on the higher center of the nervous system," which probably means that any theory to explain syncope must account for such an influence. Theories certainly may influence higher centers of the nervous system in a manner not meant in the discussion. All in all this book is extremely stimulating and should help call the attention of American physicians to an important although uncommon clinical mishap which occasionally becomes a catastrophe.

WILLIAM B. BEAN, M.D.

Ionography: Electrophoresis in Stabilized Media. By Hugh J. McDonald, M.D. Price, $6.50. Pp. 268, with 29 illustrations. The Year Book Publishers, Inc., 200 East Illinois St., Chicago 11, 1955.

This volume is written by a group who have made a number of important contributions in the field of paper electrophoresis. It represents in part a summary of work done in the author's laboratories and in part a compilation of reports in the literature.

Approximately one-fourth of the volume is devoted to a description of general experimental methods. The horizontal unit developed by the author is favored in this section, almost to the exclusion of other types of instruments.

Another fourth of the work is devoted to mobility determinations and the factors which influence them. An attempt is made to derive a relation on thermodynamic grounds for relating free solution mobility and mobility in paper-stabilized systems. However, a number of parameters which are related to "paper wetness" must be determined empirically with a standard substance whose free mobility is accurately known.

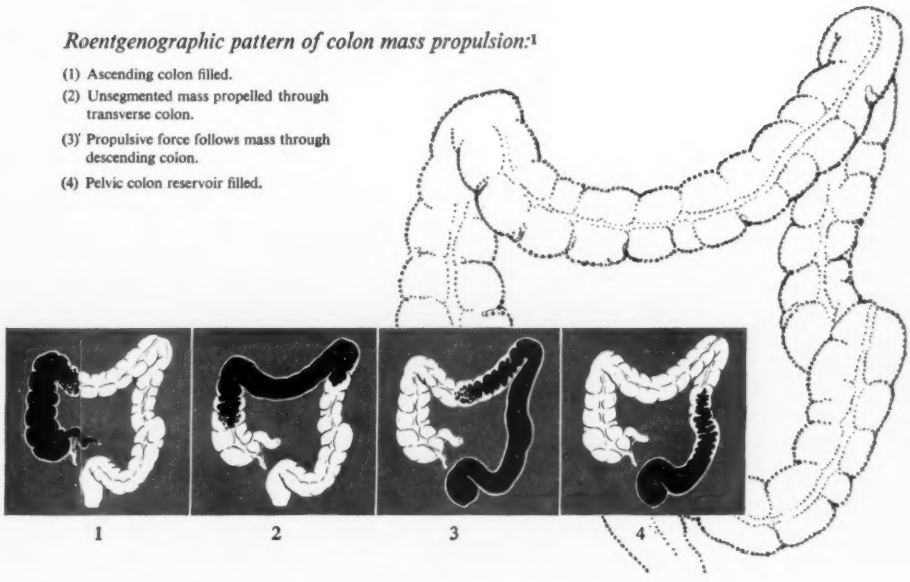
The last half of the book is devoted to a review of our present knowledge of the electromigration of substances of biological interest. The detail with which the work is reviewed varies widely. In many cases only a mention of the general nature of the investigation is made, while in other cases almost complete experimental details are given. The literature review is complete, and 865 references on electromigration in stabilized media and closely associated techniques are given.

JOHN A. D. COOPER, M.D.

SMOOTHAGE ACTION IN CONSTIPATION

Roentgenographic pattern of colon mass propulsion:[1]

(1) Ascending colon filled.
(2) Unsegmented mass propelled through transverse colon.
(3) Propulsive force follows mass through descending colon.
(4) Pelvic colon reservoir filled.



Reestablishing Bowel Reflexes with Metamucil®

Nervous fatigue, tension, injudicious diet, failure to establish regularity, too little exercise, excessive use of cathartics—all factors which contribute to constipation.[2]

Sufficient bulk and sufficient fluid form the basic rationale of treatment of constipation. Metamucil (the mucilloid of Plantago ovata) produces a bland, smooth bulk when mixed with the intestinal contents. This bulk, through its mass alone, stimulates the peristaltic reflex and thus initiates the desire to evacuate, even in patients in whom postoperative hesitancy exists.

Correction of constipation logically, therefore, lies in the suitable adjustment of such factors as nervous fatigue and tension, improper intake of fluid, improper dietary habits, failure to respond to the call to stool, lack of physical exercise and abuse of the intestinal tract through excessive use of laxatives.[2]

The characteristics of Metamucil permit the correction of most of these factors: it provides bulk; it demands adequate intake of fluids (one glass with Metamucil powder, one glass after each dose); it increases the physiologic demand to evacuate; and it does not establish a laxative "habit." Metamucil, in addition, is inert, and also nonirritating and nonallergenic.

The average adult dose is one rounded teaspoonful of Metamucil powder in a glass of cool water, milk or fruit juice, followed by an additional glass of fluid if indicated.

Metamucil is the highly refined mucilloid of Plantago ovata (50%), a seed of the psyllium group, combined with dextrose (50%) as a dispersing agent. It is supplied in containers of one pound—also four ounces and eight ounces. G. D. Searle & Co., Research in the Service of Medicine.

---

1. Best, C. H., and Taylor, N.B.: The Physiological Basis of Medical Practice: A Text in Applied Physiology, ed. 5, Baltimore, The Williams & Wilkins Company, 1950, pp. 579-583.

2. Bargen, J. A.: A Method of Improving Function of the Bowel, Gastroenterology *13*:275 (Oct.) 1949.

SEARLE

makes albuminuria detection simple, rapid

BUMINTEST®
BRAND
reagent tablets

RAPID...detects albuminuria in a few seconds

SIMPLE...no other reagents needed—no flame required

RELIABLE ROUTINE...readily-observed turbidity produced only by *clinically significant* albuminuria

Supplied in bottles of 32, 100 and 500 reagent tablets. [Reagent solution (5%) is prepared by dissolving 4 *Bumintest* Reagent tablets in 1 ounce (30 cc.) of water.]

AMES COMPANY, INC. • ELKHART, INDIANA
Ames Company of Canada, Ltd., Toronto
03786

for prothrombin time determinations . . .

Now—you can use a vial instead of a vein

Obtaining a normal control, today, can be simple. No need to hunt for "normals." No need to doubt their reliability. With a vial of Diagnostic Plasma Warner-Chilcott, you simply add distilled water to obtain a *reliable* normal control. Because of rigid standardization, Diagnostic Plasma is dependable and assures reproducible results from vial to vial and lot to lot. You can check the accuracy of Diagnostic Plasma by returning the coupon below. We'll gladly send a free trial supply.

Whether it is for prothrombin time controls or the newly important coagulase test to pinpoint pathogenic staphylococci, Diagnostic Plasma is convenient and accurate. And, it is the only lyophilized plasma, standardized for these routines, reported in the medical literature.[1-4]

Available at all leading laboratory distributors in "no-waste" vials, boxes of 10, $9.00.

References: 1. Hodes, M. E.: Clin. Chem. *5*:59 (Aug.) 1953. 2. Wollenweber, H. L.: Current M. Digest *21*:109 (March) 1954. 3. Okatvec, W. A., Jr., and Smetana, E. J.: Tech. Bull. Registry M. Tech. *24*:28 (Jan.) 1954. 4. Oktavec, W. A., Jr., and Smetana, E. J.: Am. J. Clin. Path. *24*:250 (Feb.) 1954.

Diagnostic Plasma

WARNER-CHILCOTT

WARNER-CHILCOTT

Laboratory Supply Division
113 West 18th Street
New York 11, New York

Please send a free trial supply of Diagnostic Plasma Warner-Chilcott for use in:

- ☐ Prothrombin Time Determination
- ☐ Coagulase Test

Please furnish name of local supplier ☐

name_____

institution_____

address_____

city_____ **state**_____

in rheumatoid arthritis

continuing benefits

for successful corticosteroid therapy

METICORTELONE*

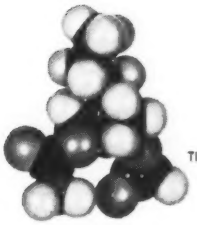
(PREDNISOLONE)

- therapy usually undisturbed by sodium retention, edema, weight gain
- excellent relief of arthritic pain, swelling, tenderness
- spares patients salt-poor diets
- up to 5 times as potent as hydrocortisone

Available as 1, 2.5, and 5 mg. tablets; 2.5 and 5 mg. capsules

METICORTELONE,* brand of prednisolone. *T. M. ML-J-66-256

Schering



THE MILTOWN MOLECULE

Two articles in the April 30th issue of The Journal of the AMA[1,2] report on . . .

an entirely new type of tranquilizer with muscle relaxant action—orally effective in

ANXIETY, TENSION and MENTAL STRESS

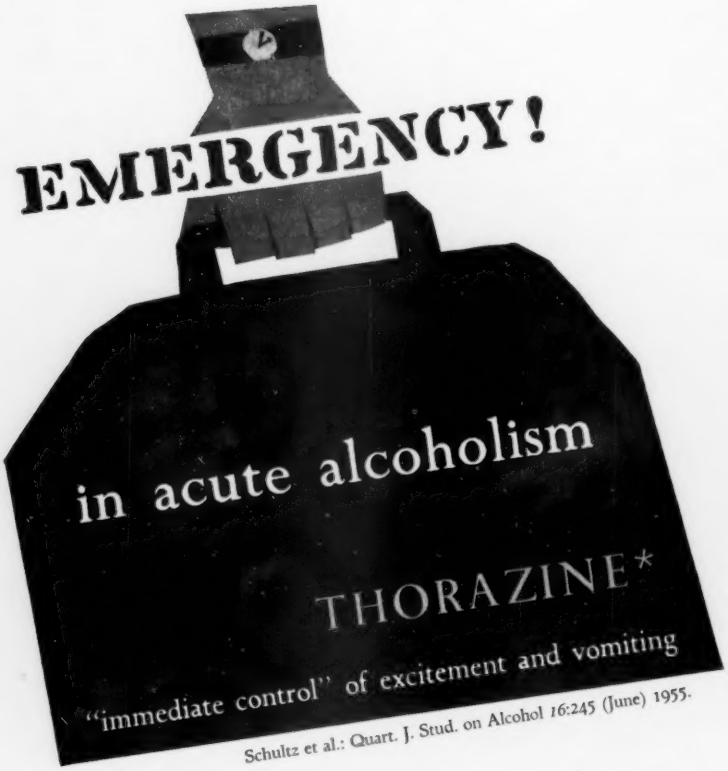
- no autonomic side effects—well tolerated
- selectively affects the thalamus
- not related to reserpine or other tranquilizers
- not habit forming, effective within 30 minutes for a period of 6 hours
- supplied in 400 mg. tablets. Usual dose: 1 or 2 tablets—3 times a day

1. Selling, L. S.: J.A.M.A. **157:** 1594, 1955. 2. Borrus, J. C.: J.A.M.A. **157:** 1596, 1955.

Miltown®

the original meprobamate—2-methyl-2-*n*-propyl-1,3-propanediol dicarbamate—U. S. Patent 2,724,720

DISCOVERED AND INTRODUCED by Wallace Laboratories, New Brunswick, N. J.
Literature and Samples Available On Request


EMERGENCY!
in acute alcoholism
THORAZINE*
"immediate control" of excitement and vomiting
Schultz et al.: Quart. J. Stud. on Alcohol 16:245 (June) 1955.

'Thorazine' is available in ampuls, tablets and syrup, as the hydrochloride; and in suppositories, as the base.

'Thorazine' should be administered discriminately; and, before prescribing, the physician should be fully conversant with the available literature.

for emergencies—always carry 'Thorazine' Ampuls in your bag

Smith, Kline & French Laboratories, Philadelphia

*T.M. Reg. U.S. Pat. Off. for chlorpromazine, S.K.F.